For Pete

Peter C. Stoker

9th Mar 1985 – 11th Dec 2007

Declaration of Authorship

I declare that the substance of this Thesis has not been submitted, nor is concurrently being submitted, in candidature for any other degree. I also declare that the work embodied in this Thesis is the result of my own investigations. Where the work of other investigators has been used, this has been fully acknowledged in the text.

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Davey A. Stoker

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G. Pattenden

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I would like to thank Professor Gerry Pattenden for his constant support, guidance and encouragement throughout my PhD, and for his patience and understanding during the compiling of this Thesis.

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I would also like to acknowledge and thank all the doctors and nurses at the Queen Elizabeth Hospital, King's Lynn, who did their utmost to look after my brother, Peter, under difficult circumstances, over the period October – December 2007.

Lastly, I thank my parents, without whose love and support I would never have been able to complete this Thesis.

Contents

Abstract

The work presented in this Thesis describes several new and novel radical macrocyclisation-transannulation cascade reactions directed towards the single step construction of ring-D aromatic steroid ring systems.

The **Introduction** introduces the steroid class of natural products, their biosynthesis and previous literature strategies towards their construction. The ring-D aromatic steroids, together with their possible total synthesis *via* a novel free-radical cascade strategy, are then discussed.

The **Results and Discussion** Chapter summarises the radical cascade strategies towards ring-D aromatic steroid ring systems that have been investigated. It is divided into two sections:

Part 1 describes the evolution of our current radical cascade approaches relating to the iododienynone precursors **117a-d** (Schemes 26-29). We proposed that the precursors **117a-d** would lead to the 6,6,6,6 ring-D aromatic steroid ring system (such as that found in the natural product nicandrenone **67**), *via* a cascade of radical ring-forming reactions. However, the proposed radical cascade from the *Z*-iododienynones **117a,c** halted at the macrocyclisation stage producing the macrocycles **137a,b**, whilst a radical cascade from the *E*-iododienynones **117b,d** instead led to the unusual bridged tricyclic structures **148a,b** and **155** (depending on whether benzene or heptane was

used as the solvent), rather than the anticipated linear tetracycles **116a,b**. A rationale for these outcomes is given.

Part 2 discusses an approach to 6,6,5,6 ring-D aromatic steroids *via* a macrocyclisation-transannulation radical cascade from the vinylcyclopropyl seleno ester precursor **193**. A synthesis of the radical precursor **193** was first examined using a novel aryl-vinylcyclopropane Stille reaction coupling protocol (the development of which is discussed), as well as several alternative routes. A practical, albeit more lengthy, synthesis of the precursor **193**, was then developed. The proposed radical cascade from the vinylcyclopropyl seleno ester **193** led to the desired ring-D aromatic steroid ring system **194a** (with the correct *trans*, *anti*, *trans* stereochemistry) together with the methyl epimer **194b**. Also isolated from the product mixture was the macrocycle **232**, together with the products of reduction and decarbonylation of the acyl radical intermediate **235**, *i.e*. **231** and **230**, and the dioxolane **233**.

The **Experimental** section describes all the procedures used to synthesise the precursor compounds **117a-d** and **193** and the products of their radical mediated cascade cyclisations. Full NMR, and other spectroscopic data, alongside mass spectrometry data are also given.

The **Appendices** include some relevant X-ray and NMR spectroscopic details.

Abbreviations

AIBN	2,2'-Azobis(isobutyronitrile)
Asp	Aspartic acid
Cp	Cyclopentyl
CuTC	Copper (I) thiophene-2-carboxylate
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DCM	Dichloromethane CH_2Cl_2
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
FPP	Farnesylpyrophosphate
His	Histidine
HMDS	*bis*-(Trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
Ile	Isoleucine
Imid	Imidazole
Leu	Leucine
NADPH	Nicotinamide adenine dinucleotide phosphate
NCS	*N*-Chlorosuccinimide
Nf	Nonaflate $-OSO_2CF_2CF_2CF_2CF_3$
NPSP	*N*-(Phenylselenyl)phthalimide
Phe	Phenylalanine
PP	Pyrophosphate
TBAF	Tetra-*n*-butylammonium fluoride

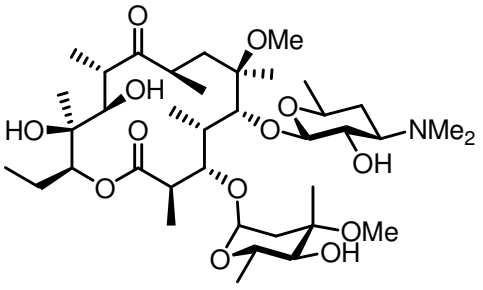
TBDPS	*tert*-Butyldiphenylsilyl $-SiPh_2C(CH_3)_3$
TES	Triethylsilyl $-Si(CH_2CH_3)_3$
Tf	Trifluoromethanesulfonyl $-SO_2CF_3$
Tol	Toluene
Trp	Tryptophan
TTMSS	Tris(trimethylsilyl)silane
Tyr	Tyrosine

Introduction

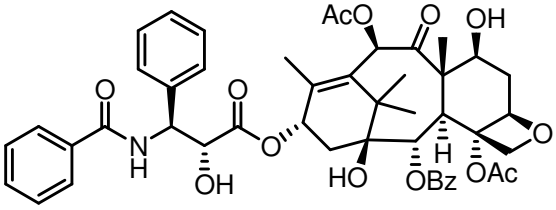
The Total Synthesis of Natural Products

Natural products have played a major role in the intellectual and experimental development of the field of organic chemistry. In the early days of chemical theory the field was concerned with structure elucidation together with the interactive and creative link between proof of structure and the advancement of the current theories. The target-oriented total synthesis of a complex natural product is still regarded by most to be the ultimate test of reaction design and application of fundamental principles.

As more and more remarkable compounds were isolated from plants, bacteria, fungi and marine sources, the imaginations of organic chemists were provoked. This, together with demands in medicine *i.e*. between 1981 and 2002, 78% of new antibacterial and 74% of new anticancer entities, such as clarithromycin **1** and paclitaxel **2**, were natural products or were natural product-derived,[1] became the driving force behind modern organic chemistry.



Clarithromycin, **1**



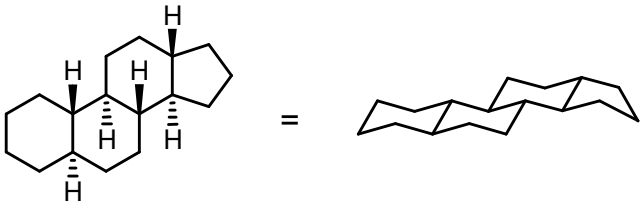
Paclitaxel, **2**

Secondary metabolites have been classified into five broad categories, depending on their biosynthetic origins, *i.e*. fatty acids and polyketides (e.g. prostaglandins and macrolides), aromatic amino acids and phenylpropanoids (e.g. lignans and flavanoids), terpenoids (e.g. taxanes), alkaloids (e.g. lysergic acid and quinolines) and peptide derivatives (e.g. penicillins and amino acids).

The terpenoids are a fascinating collection of natural products, which also include the steroids, compounds which not only have an extraordinary range of biological functions but, through the chemical study of their structures and reactions, have had a major impact on the development of organic chemistry. It is the steroid family of natural products which has particularly sparked this author's imagination, and it is the steroids which will concern the majority of this thesis.

Steroids

The steroids (from the Greek word '*stereos'*, meaning solid) are modified triterpenes containing a tetracyclic ring system **3**, which is exemplified in lanosterol **4**. This remarkably stable (samples of sediment 2.7 billion years old, have been found to contain steroids)[2] cyclopentaperhydrophenanthrene structure **3**, with its *trans*, *anti, trans, anti, trans* stereochemistry, typifies the fundamental structure of the steroids, with modifications to this structure creating a wide-range of biologically and therapeutically important compounds. For example, corticosteroids in inflammation control,[3] 19-norsteroids in reproductive regulation,[4] vitamin D metabolites as dermatological agents[5] and Na^+/K^+ pump-inhibiting cardiac glycosides from *Digitalis spp*. (first recognised as a treatment for congestive heart failure in 1775),[6] to name just a few.



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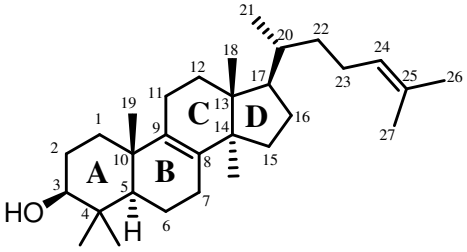


Lanosterol, **4**

Not only are the steroids fascinating structurally, and amazingly diverse biologically, they also have a remarkable biosynthesis which has captivated organic chemists and biochemists for over half a century.[7,8]

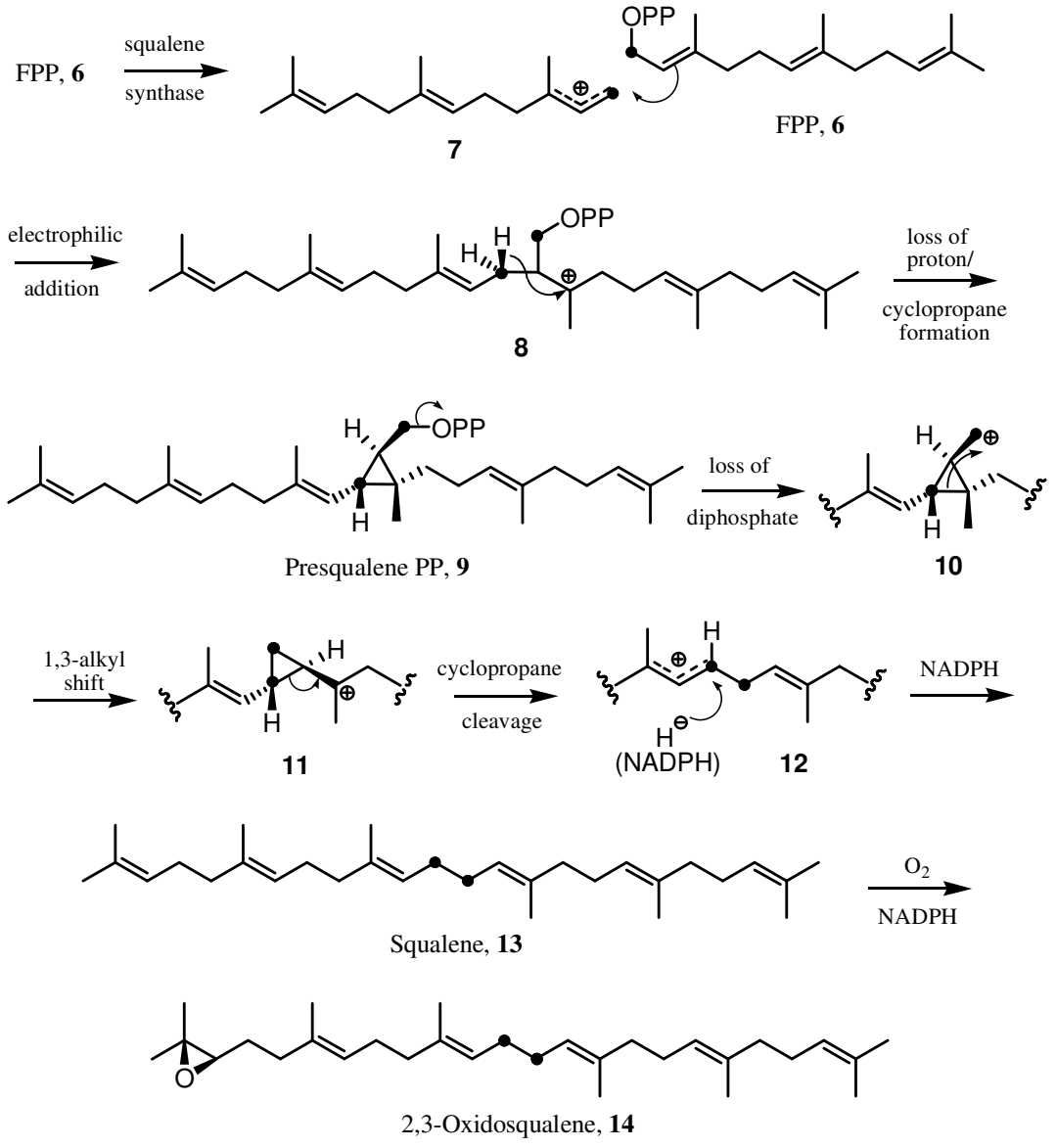
Steroid Biosynthesis

Over the last few years there have been many important advancements in our understanding of the remarkable cyclisation of oxidosqualene **14** leading to the steroids and a brief outline of the basics of steroid biosynthesis together with some of the 'new pieces to the puzzle' follow here.

The squalene cyclases occur in higher eukaryotes, and some micro organisms, and catalyse what many regard as being one of the most efficient chemical processes to have been revealed from nature. Studies with non-natural and radio-labelled substrates have established the overall pathways.[9]

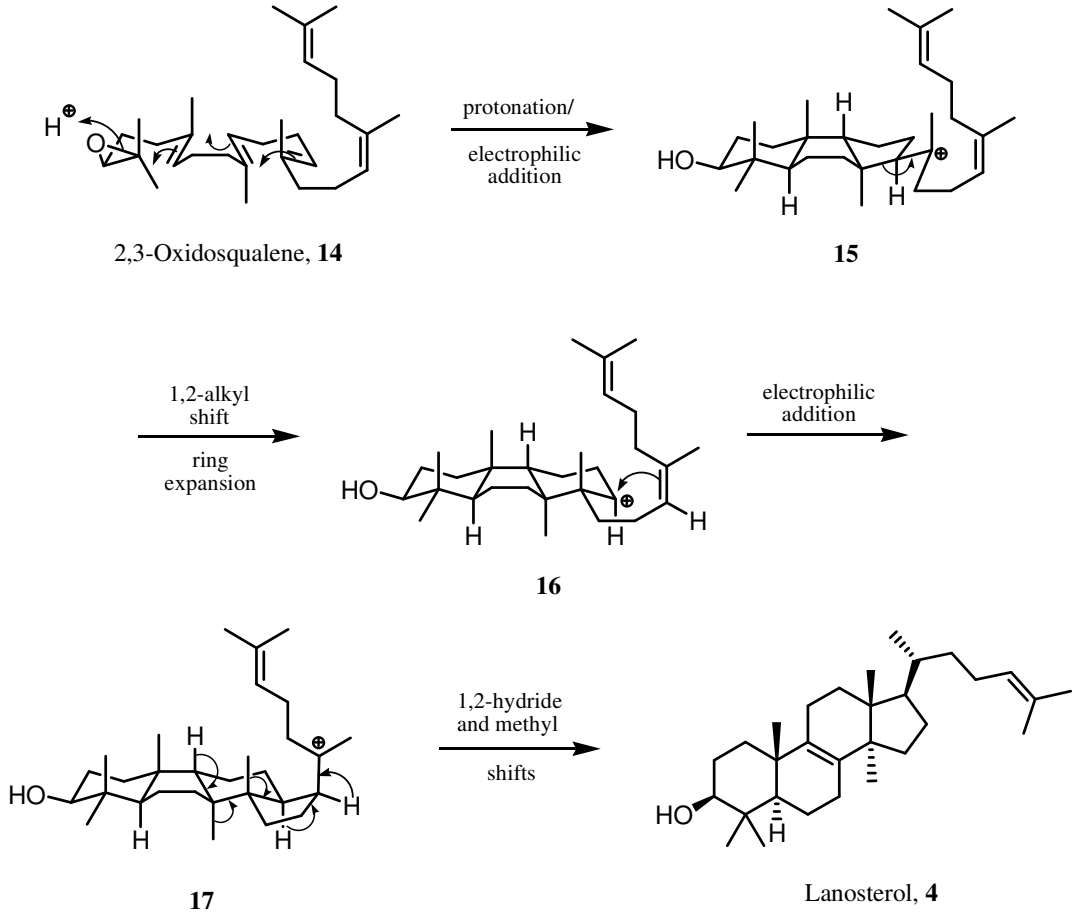
2,3-Oxidosqualene **14** is derived from farnesylpyrophosphate (FPP) **6** *via* initial attack of the 2,3-olefinic bond of FPP **6** into a second farnesyl cation **7**. The

resulting carbocation **8** next undergoes loss of a proton and concurrent cyclopropane ring formation leading to presqualene pyrophosphate **9**. Loss of the pyrophosphate group from presqualene PP **9** then gives a cyclopropylmethyl primary cation **10** which, *via* a Wagner-Meerwein 1,3-alkyl shift, generates the more stable tertiary carbocation species **11**. Finally, cleavage of the cyclopropane in **11** leads to an allylic carbocation **12** which is quenched by NADPH, to give squalene **13**. A flavoprotein mono-oxygenation of **13** then gives 2,3-oxidosqualene **14** (Scheme 1).[10]



Scheme 1 The biosynthesis of 2,3-oxidosqualene **14**

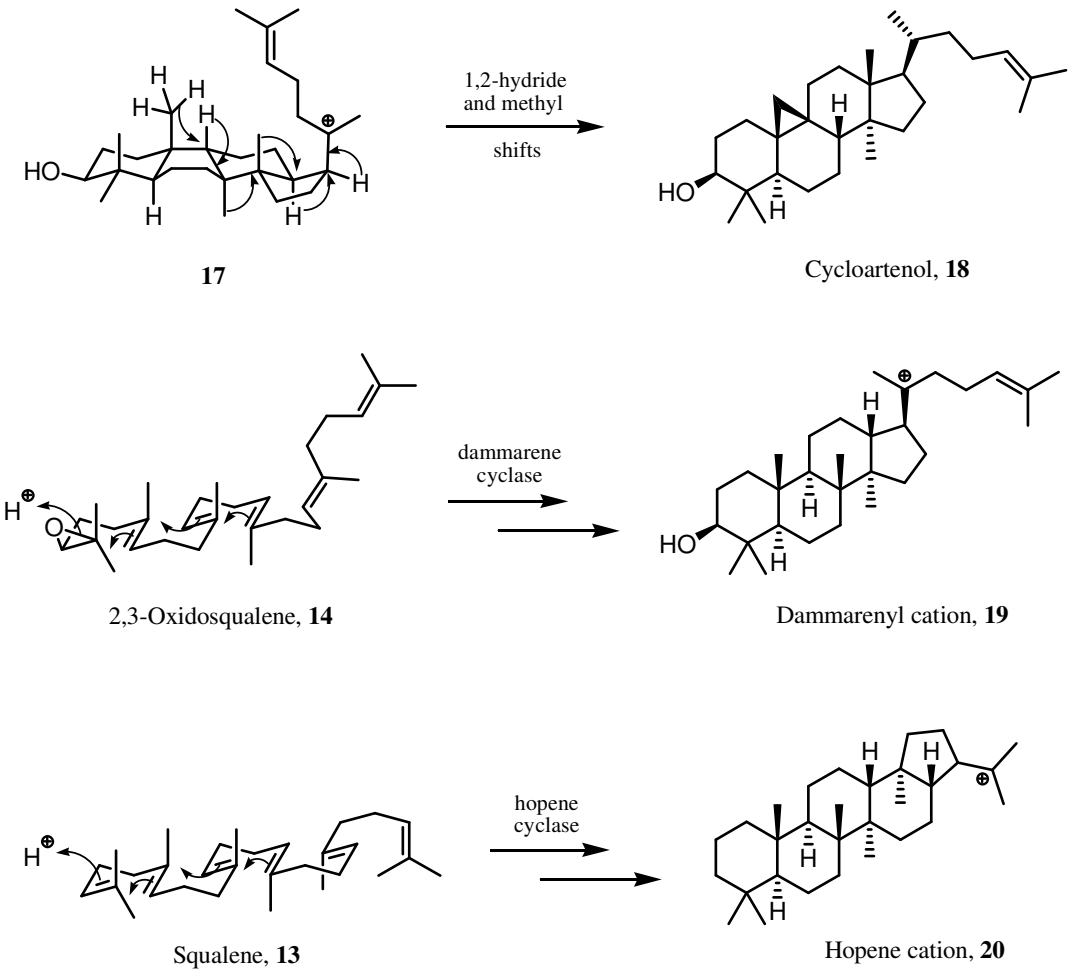
Oxidosqualene **14** binds to the active site of an oxidosqualene cyclase enzyme, folding as it enters the 'pocket', into a chair-boat-chair-boat conformation. The cyclisation is initiated by protonation of the epoxide which allows the first three rings in the steroid to be formed, *via* a 6-*exo*-tet and two 6-*endo*-trig cyclisations. The resulting tricyclic carbocation **15**, however is associated with a five-membered ring C, which then undergoes a 1,2-alkyl shift with concomitant ring expansion to give the expected six-membered ring tricyclic **16**.[11,12] A further electrophilic addition results in the formation of the five-membered D-ring tetracyclic carbocation **17**. The final stages in the biosynthesis of lanosterol **4** from **14** involve a series of 1,2-hydride and 1,2-methyl shifts to give the familiar steroidal stereo pattern (Scheme 2).



2,3-Oxidosqualene, **14** — **15** — **16** — **17** — Lanosterol, **4**

Scheme 2 The biosynthesis of lanosterol **4** from 2,3-oxidosqualene **14**

There are many variations of this fascinating process in nature. For example, whilst the above process is typical for animals and fungi, in plants H-9 is not lost from **17** to produce the olefinic B/C ring bridge, but rather the H-19 proton is lost producing cycloartenol **18** instead. There are also various "hopene" and "dammarene" cyclases producing pentacyclic hopenes **20** and dammarenoids **19** respectively, as well as hundreds of other variations which have fashioned nature with thousands and thousands of polycyclic triterpenoids which are utilised in a near countless number of biological processes (Scheme 3).



17 Cycloartenol, **18**

2,3-Oxidosqualene, **14** Dammarenyl cation, **19**

Squalene, **13** Hopene cation, **20**

Scheme 3 The biosynthesis of cycloartenol **18** and the dammarenoids **19** and hopenoids **20**.

Recent findings, involving crystallographic and structure-based mutagenesis studies, have provided two important additional 'snapshots' of the aforementioned cascade process leading to steroids, and have begun to reveal intimate structural details of the catalytic mechanism. Reinert *et al*. for example, have determined the structure of the hopene cyclase active site complexed with a squalene mimic,[13] and Thoma *et al*. have determined the structure of human oxidosqualene cyclase complexed with lanosterol **4**.[14] These results are summarised below in Figure 1 using hopene cyclase as an example.[15]

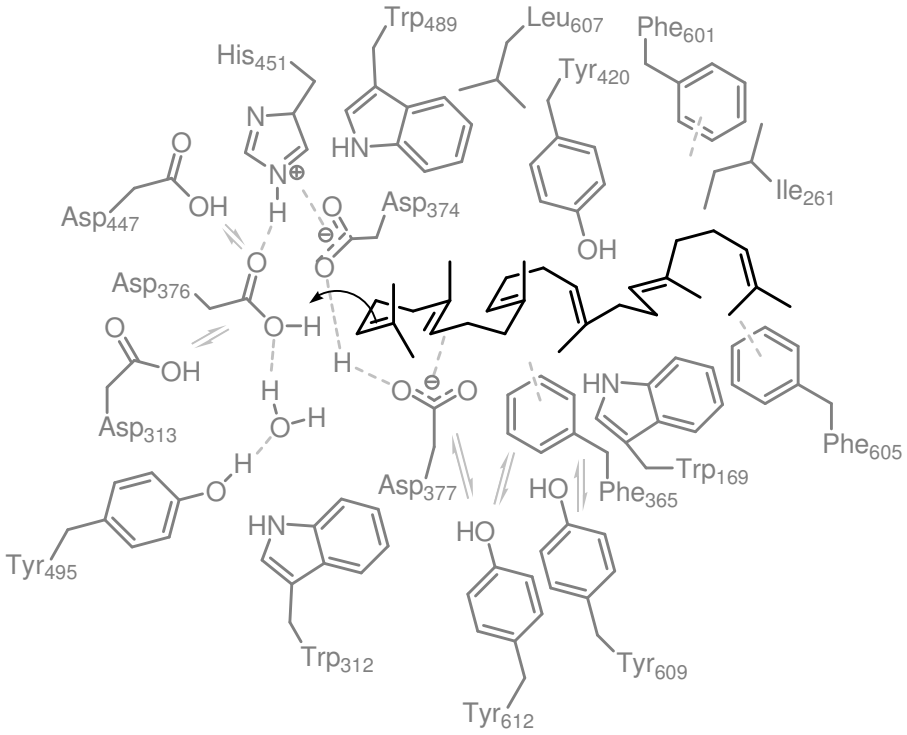


Figure 1 The active site of squalene-hopene cyclase

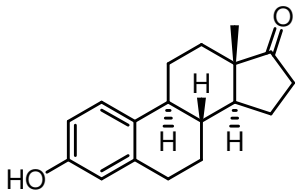
Briefly, we now know that an aspartic acid residue (asp 376) polarised by a positive histidine residue (his 451) initiates the cascade cyclisations by protonation. Asp 447,313 and tyr 495 then reprotonate asp 376 as the cation moves away, along the squalene molecule. There then follows a complex series of interactions between

the various intermediate cations and the remaining surrounding residues. For example, phe 601,365,605, asp 377, trp 489 and tyr 420,612,609 are involved in carbocation stabilisation mostly *via* non-bonding interactions, ile 261 is instrumental in stereocontrol, and trp 312,169 and leu 607 control substrate binding.[16,17]

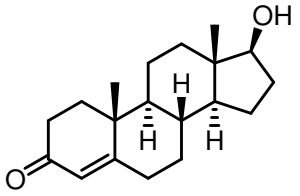
Having such a diverse range of potential pharmaceutical applications it should come as no surprise that chemists have tried to emulate nature by synthesising various steroids for therapeutic applications. For thirty years, after world war two, the study and synthesis of steroids was a major field of research. These studies have contributed to our understanding of basic chemical principles, chemo- and stereo-selectivity, orbital alignment and the chemistry of polycyclic ring systems. They have also furnished us with several new reagents and named reactions. We shall now outline some of the main strategies that have been used so far to synthesise steroids *in vitro*.

The Synthesis of Steroids

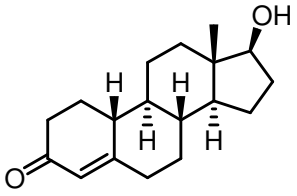
The immense structural and bio-diversity found in the steroids (*i.e.* the sexual hormones estrone **21** and testosterone **22**, the metabolic growth hormone nandrolone **23** and the synthetic anti-inflammatory pro-drug prednisolone **24**)[18] has resulted in a copious number of approaches and strategies towards their synthesis. The complex stereochemistry and the well-defined ring structure, together with their various physiological activities make the steroids an interesting challenge for synthetic chemists.[19] A short historical overview and some highlights in steroid synthesis are given below.



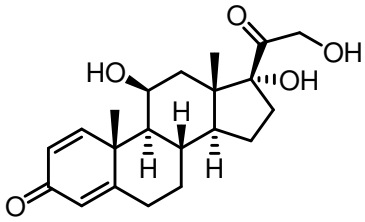
Estrone, **21**



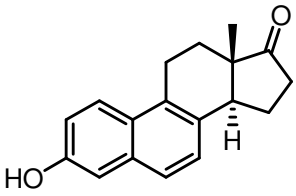
Testosterone, **22**



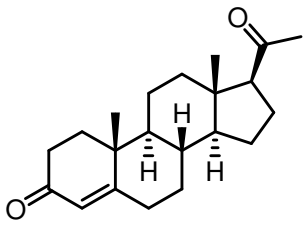
Nandrolone, **23**



Prednisolone, **24**



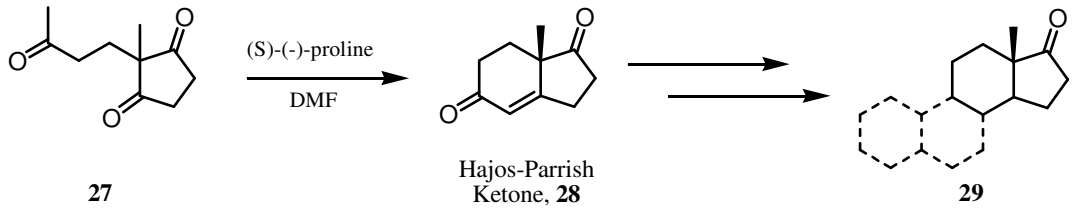
Equilenin, **25**



Progesterone, **26**

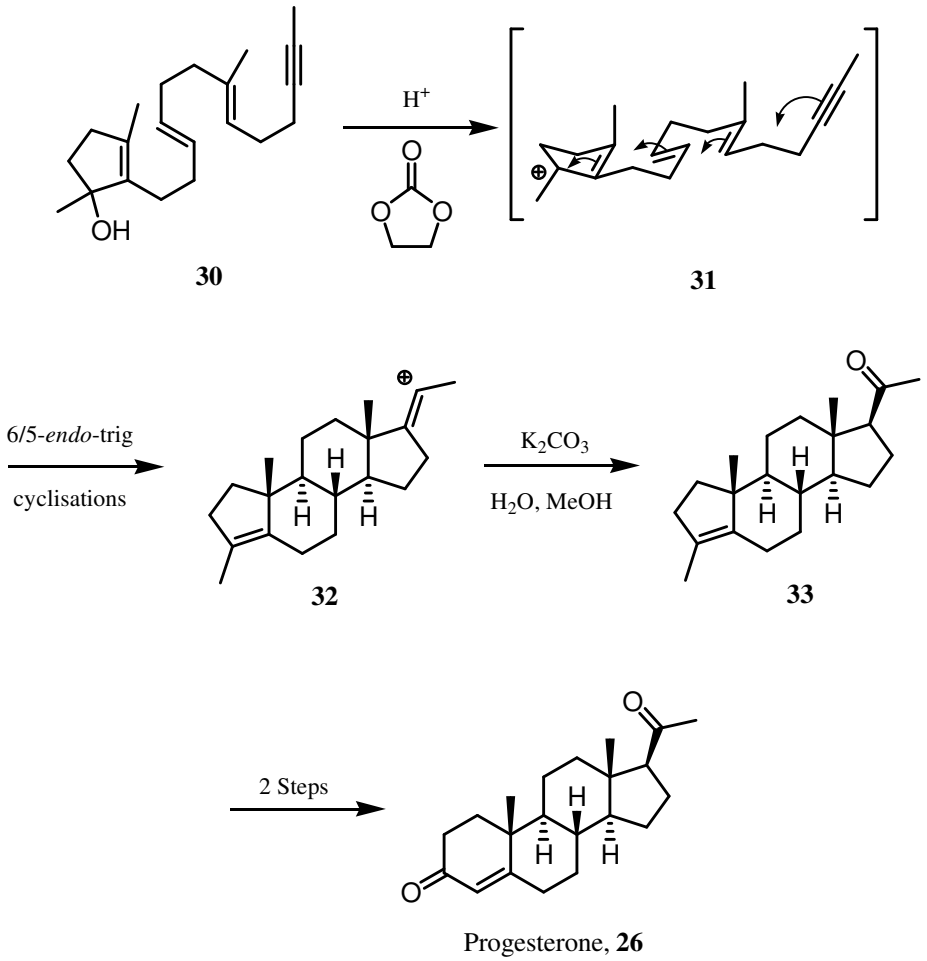
The first total synthesis of a steroid was that of the naphthalene-based equilenin **25** by Bachmann *et al*. in 1939.[20] This was followed by the milestone synthesis of estrone **21** in 1948 by Anner and Miescher.[21] Since then several novel and powerful strategies have been developed to combat the multifaceted structure found in the steroidal core.

Early strategies were mostly based on the Robinson-annulation reaction which became more applicable with the discovery of the enantioselective Hajos-Parrish reaction allowing access to a building block for the C/D rings (Scheme 4).[22]



Scheme 4 The Robinson-annulation strategy towards steroids

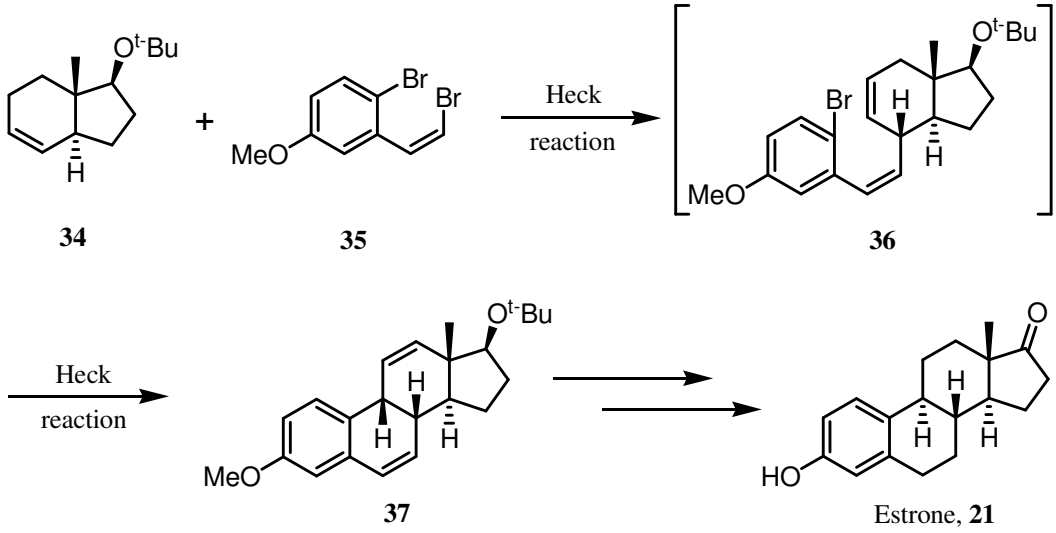
In 1971 Johnson *et al*. published their pioneering biomimetic synthesis of progesterone **26**.[23] This 'classic' synthesis involves the construction of the steroid framework **33** in one step, from a linear squalene inspired precursor **30**, *via* a Lewis acid catalysed polyolefinic cyclisation (Scheme 5).



Scheme 5 Johnson's biomimetic synthesis of progesterone **26**

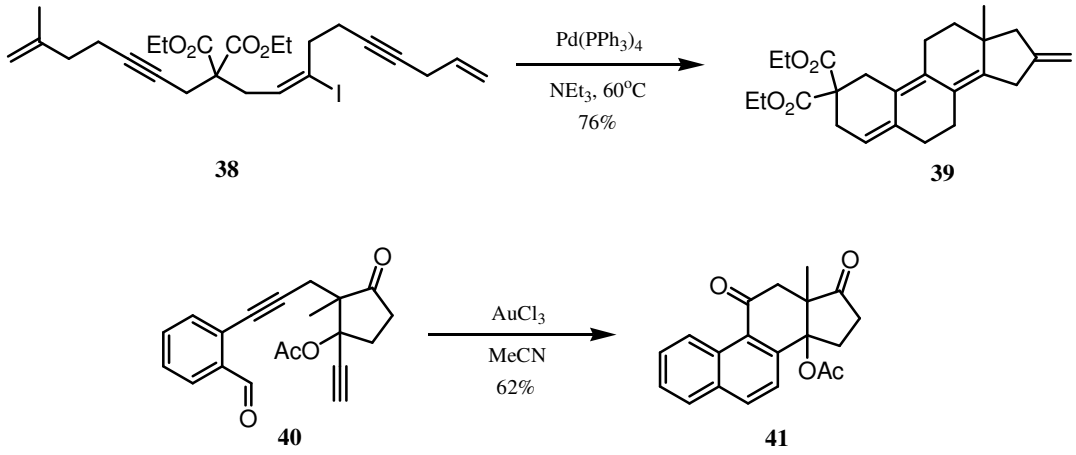
The cascading 6/5-*endo*-trig cyclisations gave a 5:1 selectivity for the desired isomer of **33** according to the Stork-Eschenmoser hypothesis.[24] Enantioselective versions of this strategy were later developed.[25,26]

Cascade reactions exploiting transition metal mediated cyclisations have also been utilised as an approach to synthesising the steroids. For example, the total synthesis of estrone **21** by Tietze *et al*. involves a double Heck cyclisation of the dibromide **35** and the olefin **34** (derived from the Hajos-Parrish ketone **28**) as the key step (Scheme 6).[27]



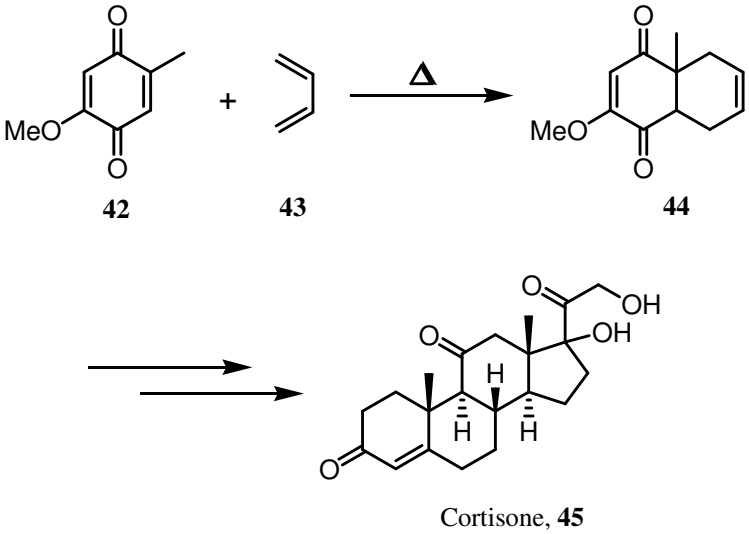
Scheme 6 A total synthesis of estrone **21** by Tietze *et al*.

A palladium catalysed polyene cyclisation cascade of the iodide **38** by Negishi *et al*., delivers the steroidal-like polycycle **39** in a single step,[28] and the recent gold catalysed cascade of the aldehyde **40**, by Dyker *et al*.,[29] to give the steroidal framework **41**, are also good examples of the use of transition metal mediated reactions in the creation of steroids (Scheme 7).



Scheme 7 Transition metal mediated cyclisation strategies

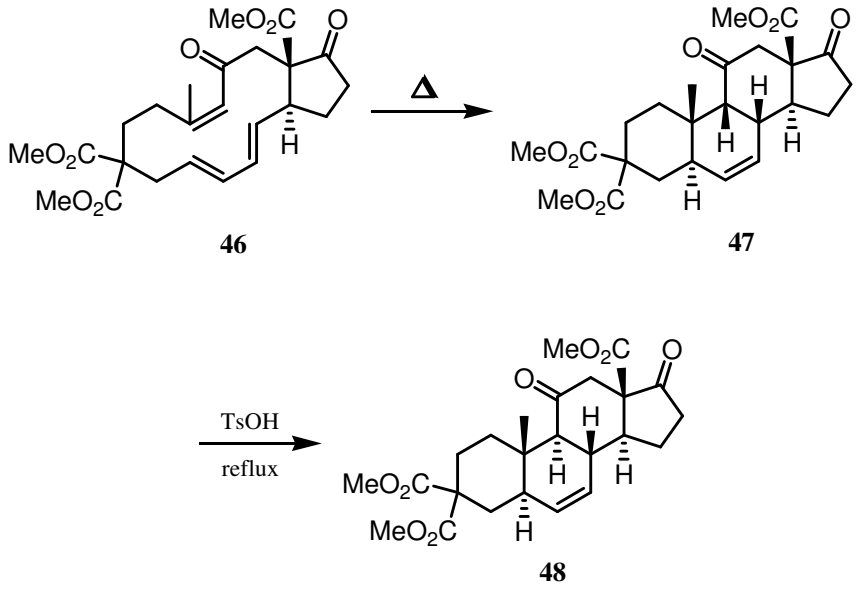
The Diels-Alder reaction,[30] a powerful technique for the construction of six membered rings with the concurrent formation of two new carbon-carbon bonds and up to four new stereocenters in a single step has, unsurprisingly, been exploited in the synthesis of steroids.



Scheme 8 Woodward's synthesis of cortisone **45** *via* a Diels-Alder strategy.

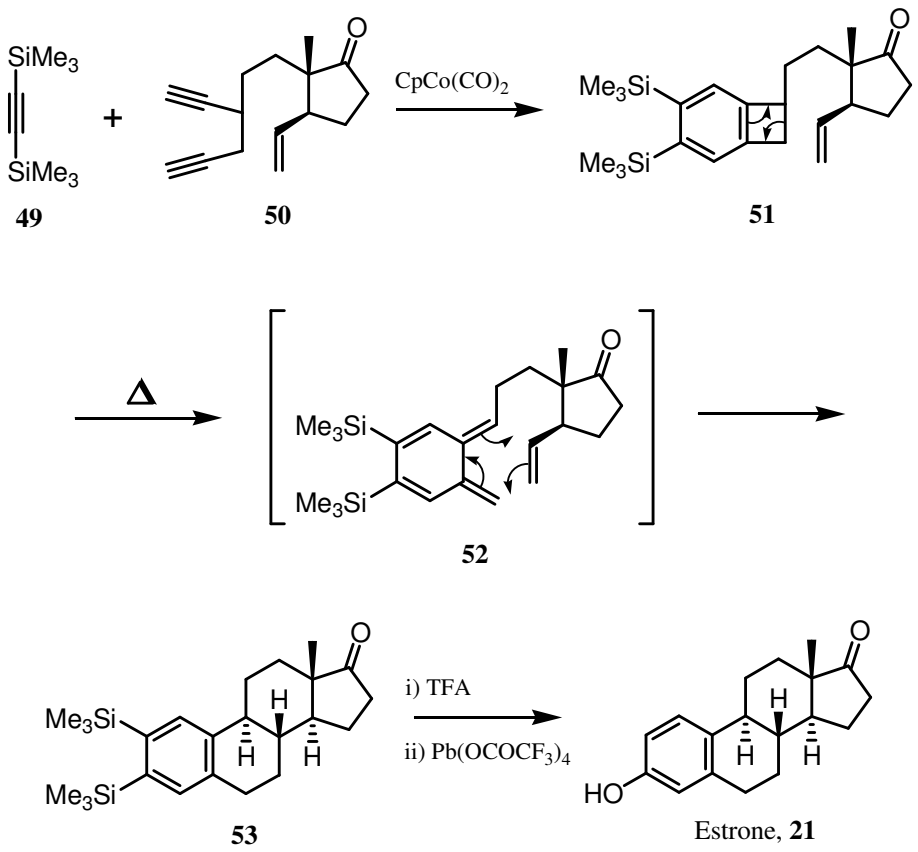
In 1952, Woodward *et al*. constructed the A/B rings *via* an intermolecular Diels-Alder reaction in a total synthesis of cortisone **45** (Scheme 8).[31]

The intramolecular Diels-Alder reaction has been exploited to the utmost in polycycle synthesis by Deslongchamps *et al*. The example shown below demonstrates that the crucial *trans* stereochemistry of the steroids cannot be accessed directly *via* this strategy, but that this can be solved by a subsequent epimerisation of the Diels-Alder product **47** (Scheme 9).[32,33]



Scheme 9 Deslongchamps' steroid synthesis *via* a transannular Diels-Alder strategy.

Of special interest is the 'classic' synthesis of estrone **21** by Vollhardt *et al*.[34] In this novel strategy Vollhardt generates the intramolecular Diels-Alder *o*-quinodimethane precursor **52**[35] *via* a thermolytic opening of benzocyclobutene **51** (prepared by a cobalt catalysed cyclotrimerisation of dialkyne **50** and alkyne **49**). This single step reaction generates the B- and C-rings of **53** with the correct relative stereochemistry. A further two steps lead to estrone **21** (Scheme 10).[36]



Scheme 10 A total synthesis of estrone **21** by Vollhardt *et al*.

The Pattenden group has had a particular interest in cascade radical chemistry from polyenes leading to steroids for a number of years, and we shall now introduce this strategy for synthesising the steroids.

A Free Radical Cascade Approach to the Steroids

The current approach to steroids *via* cascade radical cyclisation has been developed over the last twenty years by our group in Nottingham, and others, and it has become a powerful method for the construction of polycyclic systems. A cascade reaction (sometimes referred to as a 'domino' reaction) is a multistep 'one-pot' sequence whereby the first step creates the functionality for the second step, the

second for the third, and so on. This is exactly what occurs in a correctly setup polyolefinic system when a suitable carbon radical centre is generated.[37]

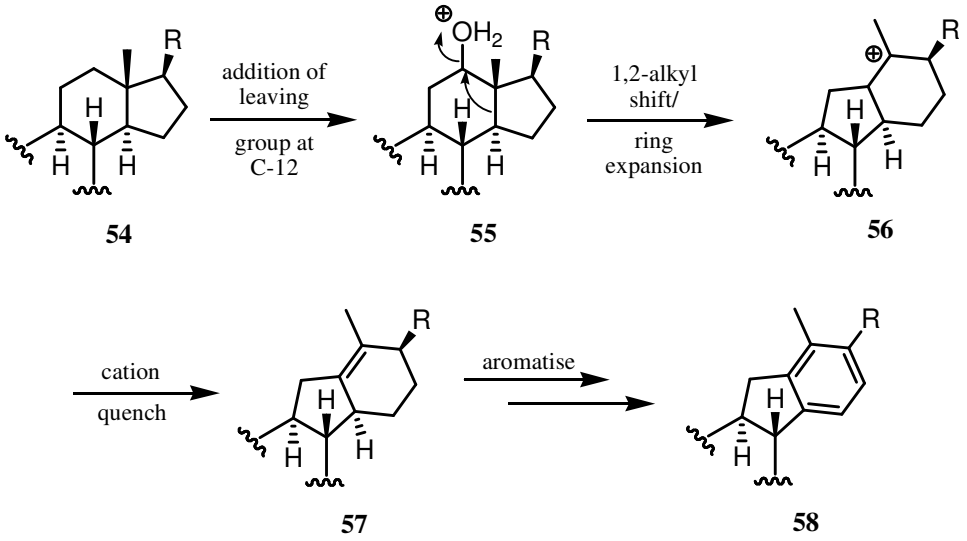
Radical chemistry, compared to anionic and cationic chemistry is, relatively speaking, still in its infancy having had a lengthy gestation period. Since the first carbon centred radical was discovered in 1900 by Gomberg,[38] radical reactions have mostly been perceived as difficult to control, very unselective, and only of use in a few polymerisation reactions. However, we know today that radical chemistry can be a powerful tool in organic synthesis and that the radical cascade especially, could arguably be described as a highly efficient, mild, clean, and yet functionally tolerant reaction. Indeed, due to the large amount of rate constant data collected on radical reactions,[39] radical-molecule reactions can have a higher level of predictability in complex settings than most other types of reaction. Radicals are now highly valued synthetic intermediates, often used for transformations that are difficult to accomplish by other means (*i.e.* the kinds of functional group protections so often required for ionic reactions are rarely required in radical mediated reactions).[40]

There are numerous books and reviews on the use of radicals in organic synthesis and several of these are found in ref.41.

The evolution of the current radical cascade strategy to steroids will be discussed in the following sections. First however, we shall introduce the fascinating sub-class of steroids that have an aromatic ring replacing the more normal cyclopentane D-ring *i.e*. ring-D aromatic steroids.

Ring-D Aromatic Steroids

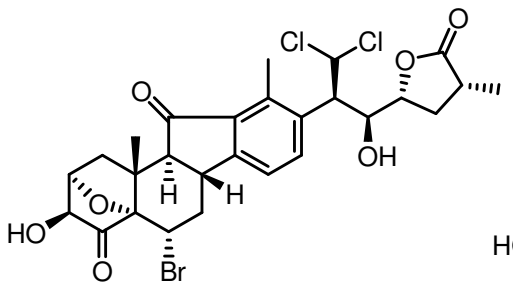
There are two different types of ring-D aromatic steroid, which arise from two different biosynthetic modifications of the typical 6,6,6,5 steroid skeleton. The first type are the 6,6,5,6 ring-D aromatic steroids. These have a five membered ring-C as well as the 6-membered aromatic ring-D, and arise *via* the simultaneous ring expansion of the D ring and contraction of the C ring.



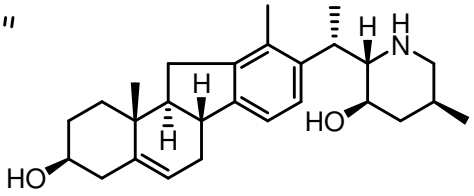
Scheme 11 A proposed biosynthetic route to the 6,6,5,6 ring-D aromatic steroids

The current understanding of this biosynthetic process is that it initiates with the addition of a leaving group at C-12, most probably a protonated hydroxyl group. A 1,2-alkyl shift, on cation **55**, then gives the 6-membered ring-D tertiary carbocation **56**. Elimination of a proton results in the alkene **57** commonly found in the veratrum alkaloids, such as jervine and cyclopamine, and further oxidation of the same ring leads to the aromatic D-ring **58** (Scheme 11).[42,6]

Two prominent examples of 6,6,5,6 ring-D aromatic steroids are nakiterpiosinone **59** and veratramine **60**.



Nakiterpiosinone, **59**

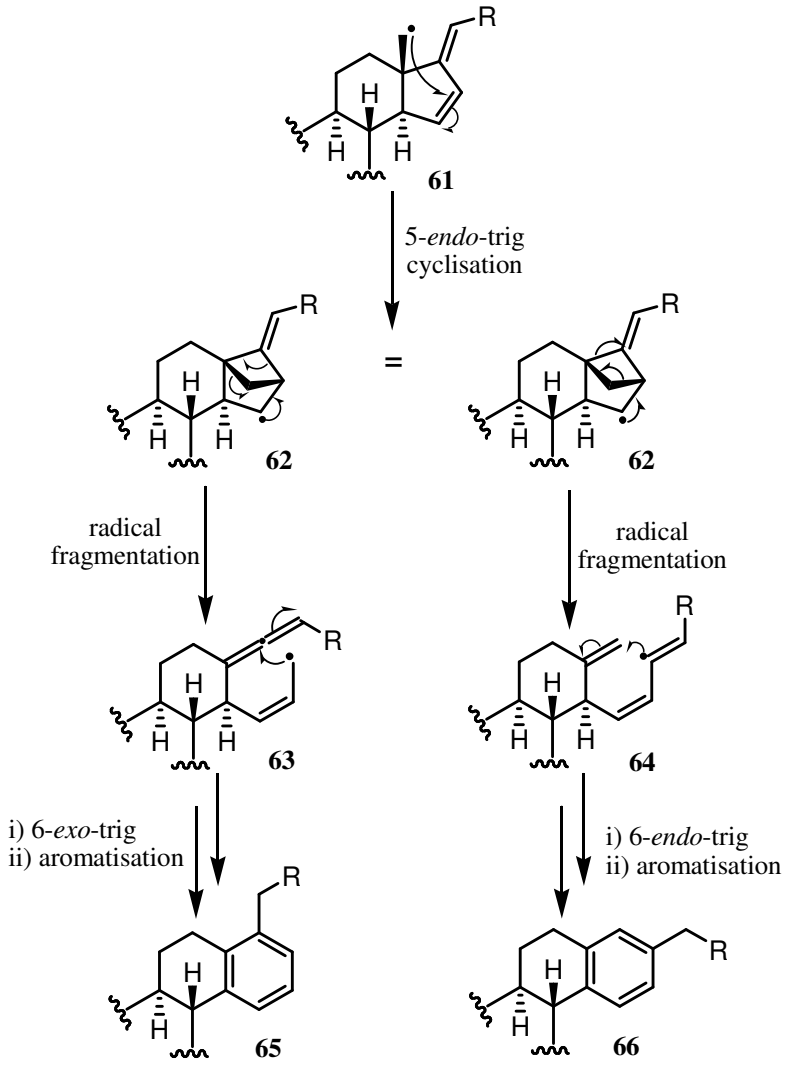


Veratramine, **60**

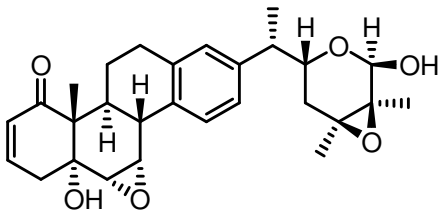
Nakiterpiosinone **59** is a cytotoxic ring-D aromatic steroid isolated in 2004 by Uemura *et al*., from the marine sponge *Terpios hoshinota*, off the coast of the Ryukyu Islands.[43] This was the first ring-D aromatic steroid to be isolated from a marine source. Veratramine **60** was isolated from the white hellebore (*Veratrum grandiflorum*) by Saito *et al*. in 1940.[44] This steroidal alkaloid is biologically active as an anti-accelerator of the heart,[45] an antagonist to the cardiovascular action of epinephrine[46] and as an excitor of the central nervous system.[47] There is also evidence to suggest that veratramine **60** is a potent non-teratogenic toxin[48] (the only non-teratogenic veratrum alkaloid to be isolated).

The second type of ring-D aromatic steroid, which we shall discuss has a 6,6,6,6 steroidal carbon skeleton *i.e*. they retain the six-membered C-ring whilst expanding and aromatising the D-ring. Nicandrenone **67** is the most prominent example of this class of ring-D aromatic steroid. The steroid was first isolated from the Peruvian 'shoofly' plant *Nicandra physaloides* in 1951 by Gizycki and Kotitschke,[49] but it was not until Yamamato *et al*. made a separate study in 1964[50] that the two groups from the UK[51] and US[52] became interested in the potent anti-feedant properties of

this steroid. Whilst precise details of the biosynthesis of these steroids are unknown, it seems plausible that at some point the angular C-18 methyl in a 'regular' steroid becomes incorporated into the D-ring. Whiting *et al*. carried out numerous studies on the nicandrenoids and proposed a free-radical biosynthetic mechanism for the expansion and aromatisation of the D-ring.[53] These authors proposed that if a radical is generated at C-18 this could attack an oxidised ring-D to give a bridged D-ring intermediate **62**. This intermediate **62** could then fragment in two different ways resulting in a 6,6,6,6 ring-D aromatic steroid with two different methyl substitution patterns **65/66** (Scheme 12).[54]



Scheme 12 Whiting's proposed biosynthetic route to the 6,6,6,6 ring-D aromatic steroids



Nicandrenone, **67**

This Thesis details our efforts to synthesis the core 6,6,6,6 and 6,6,5,6 ring systems in aromatic D-ring steroids, such as nicandrenone **67** and veratramine **60**, *via* a free radical cascade strategy. These studies are described in the Results and Discussion sections, which now follow.

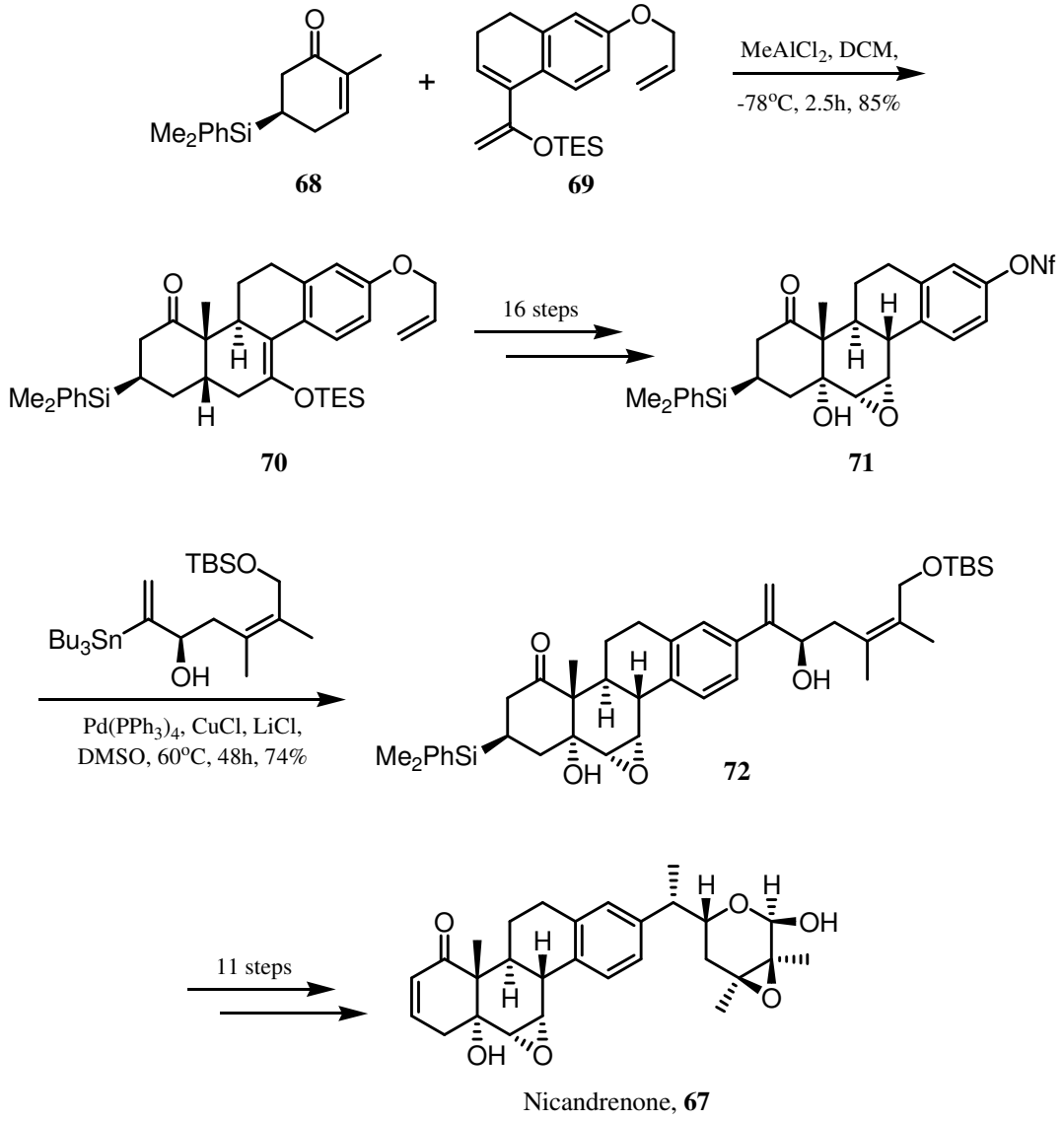
Results and Discussion

Part 1

A Cascade Radical-Mediated Approach

towards Nicandrenone

The family of insect antifeedant compounds known as the nicandrenones (or NICs), *e.g.* nicandrenone or NIC-1 (**67**), isolated from the Peruvian "shoofly" plant *Nicandra physaloides*,[49,50] are probably the best-known group of naturally occurring ring-D aromatic steroids.[51,55] Although some detailed studies have been conducted to determine the possible origin of the aromatic D-ring in these compounds (see pages 18-20), relatively little attention has been given to their total synthesis.



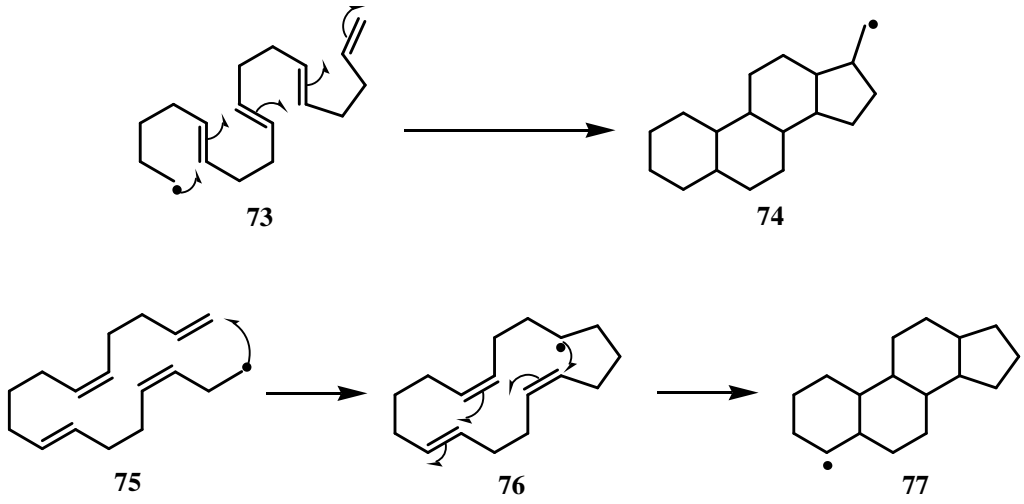
Scheme 13 Corey's total synthesis of nicandrenone **67**

Until 2000 no member of either the nicandrenones (or the structurally related withanolides), had been completed by total synthesis. Corey *et al*. describe the only total synthesis of nicandrenone[56] utilising as the key step, a Diels-Alder reaction which constructed the B-ring in the key intermediate **70**. This highly unusual *exo*-selective Diels-Alder reaction[57] was followed by a further sixteen steps which elaborated the complex pattern of functionality found in the A- and B-rings of nicandrenone **67**. The side chain in the natural product was then coupled with the intermediate nonaflate **71** in a Stille reaction, and a further eleven steps were then required to expand the functionality of the side-chain and complete the synthesis of nicandrenone **67** (Scheme 13).

Our strategy for synthesising a ring-D aromatic steroid such as nicandrenone **67**, involved a free-radical cascade as the key step, and we shall now discuss the development of this strategy to its current state.

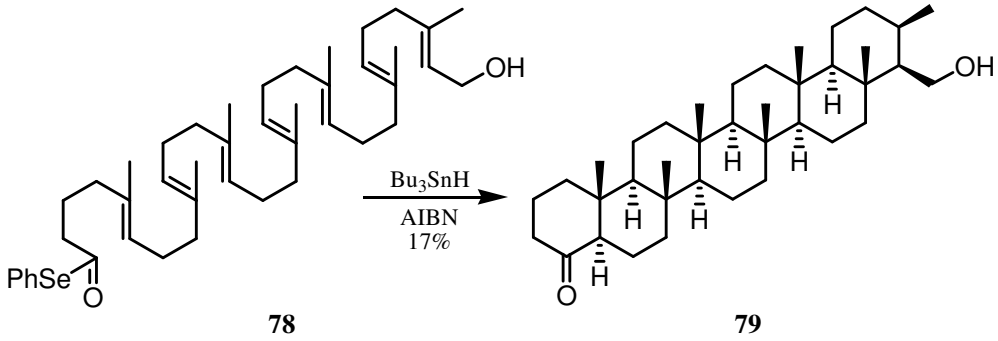
The Development of a Radical Cascade Strategy towards Ring-D Aromatic Steroids

In general, there are two different approaches towards constructing a polycycle *via* a radical cascade: i) a sequential ring closing cascade based on **73→74**, and ii) a macrocyclisation followed by a series of transannulation reactions e.g. **75→77** (Scheme 14).



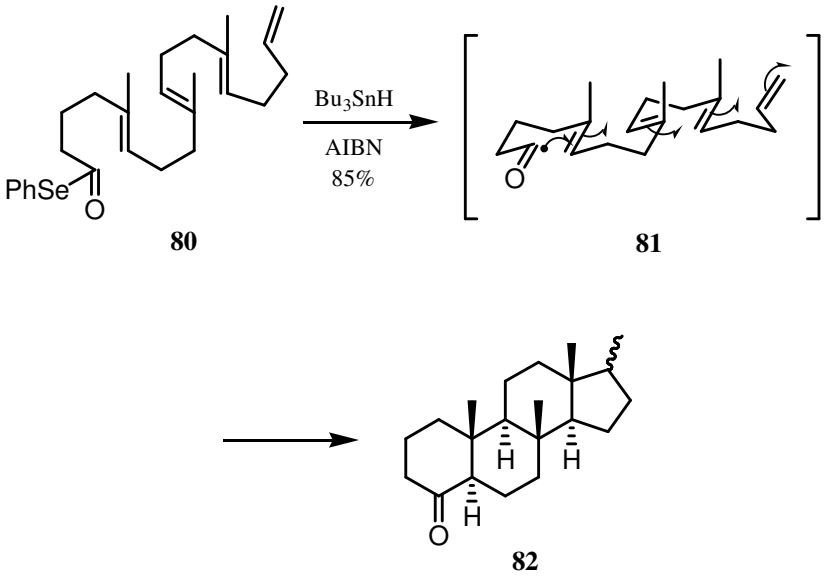
Scheme 14 Approaches for the construction of polycycles *via* radical cascades.

A unique and powerful example of the sequential approach has been developed by our research group. Judicious forward planning allowed the polyene **78**, when subjected to the radical generating conditions of tributyltin hydride and AIBN, to undergo seven consecutive cascading 6-*endo*-trig cyclisations, creating seven new carbon-carbon bonds and fourteen new stereocenters within the product heptacycle **79**.[58] This example forms a persuasive argument for the merit of this approach in organic synthesis (Scheme 15).



Scheme 15 Nottingham's sequential radical cascade approach to the heptacycle **79**.

Our research group has also demonstrated that the consecutive radical cascade approach can also be used to synthesise the steroid ring core in high yield. For example, when the acyl radical **81** was generated from the phenylseleno ester **80**, the tetracycle **82** was produced, in 85% yield (Scheme 16).[59]



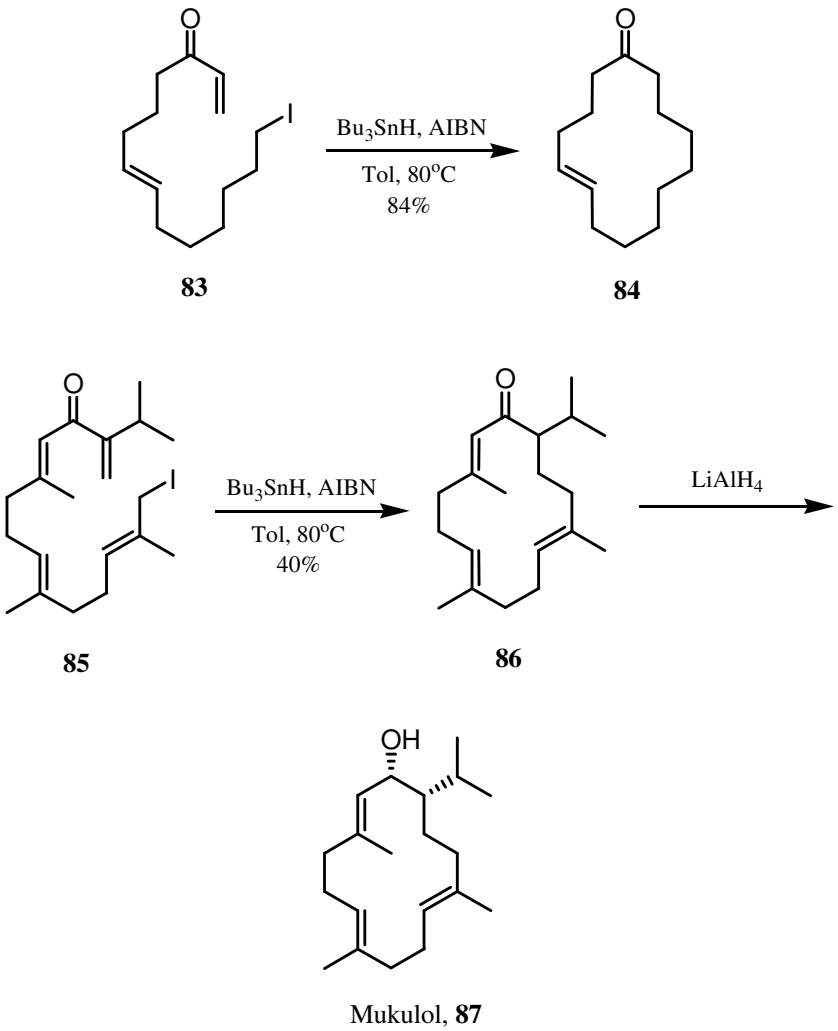
80 **81** **82**

Scheme 16 A Synthesis of the steroid ring core *via* a sequential radical cascade.

The majority of the work contained within this thesis however utilizes the second approach (the macrocyclisation-transannulation cascade) and we shall now concentrate on how this strategy developed before and during the period of my studies.

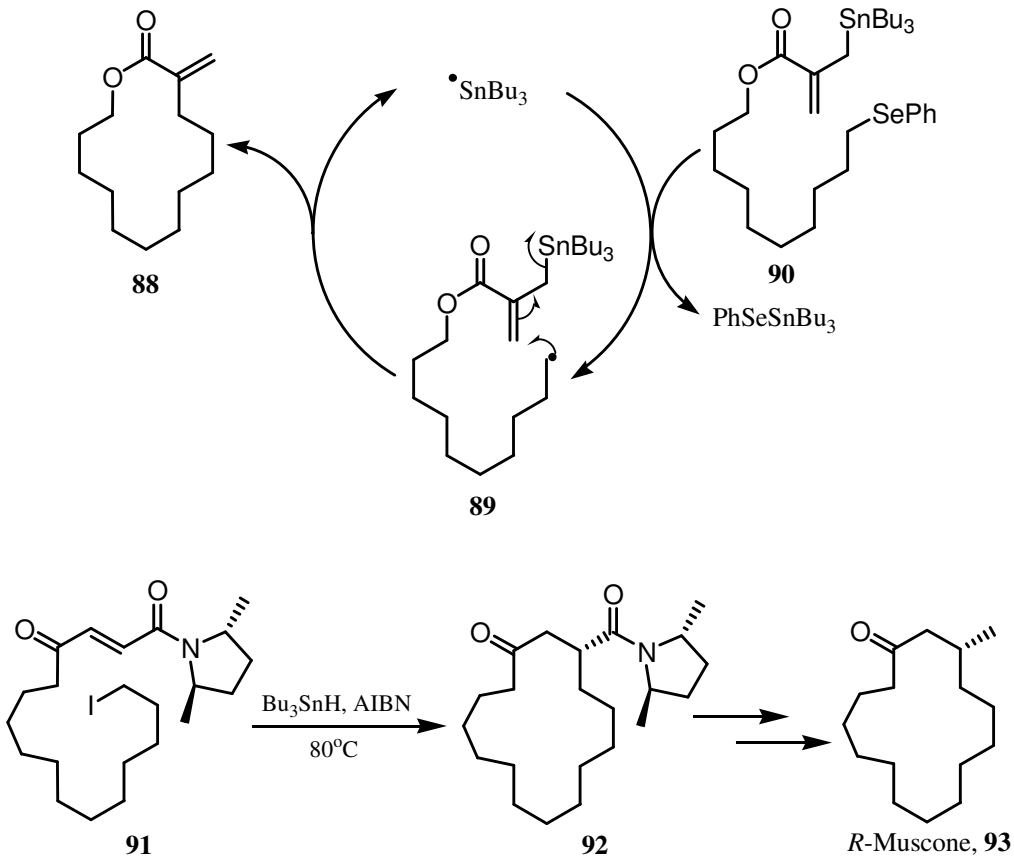
The first significant work in this area was published by Porter *et al*. who determined that for an efficient macrocyclisation of an alkyl radical to take place, the unsaturation undergoing attack would need to be electron deficient (to improve SOMO-LUMO overlap). Furthermore, alkyl iodides should be used as the radical precursors, and the radical cascade should be carried out under high dilution conditions (so as to minimize bimolecular radical reactions) and the enone system

should be used as the radical acceptor (electrophore).[60] Restricting the conformation of the macrocycle (and therefore lowering the steric repulsion and entropy of the transition state) was also found to significantly promote radical macrocyclisation.[61] For example, the 14-*endo*-trig radical macrocyclisation of the iodide **83** studied by Porter *et al.* was optimized according to the above guidelines and the reaction occurred in good yield.[62] The Pattenden group subsequently exploited the radical macrocyclisation to good effect in a total synthesis of mukalol **87**, a macrocyclic terpene natural product ideally suited for this method (Scheme 17).[63]



Scheme 17 Some Radical macrocyclisations in organic synthesis.

More recently, catalytic and enantioselective variants of the radical macrocyclisation have been developed. Baldwin *et al*. developed a catalytic radical macrocyclisation using an alkyl selenide as the precursor and an allylic stannane as the electrophore. For example the selenide **90**, when treated with catalytic amounts of stannyl radical resulted in the alkyl radical **89** which then underwent radical macrocyclisation to give the macrocycle **88**.[64] Interestingly, the possibility for direct reduction (possibly the foremost potential problem that must be considered when planning a radical reaction) was almost eliminated in this type of system due to the *in situ* generation of the stannyl radical in catalytic amounts.



Scheme 18 Catalytic and enantioselective variants of the radical macrocyclisation.

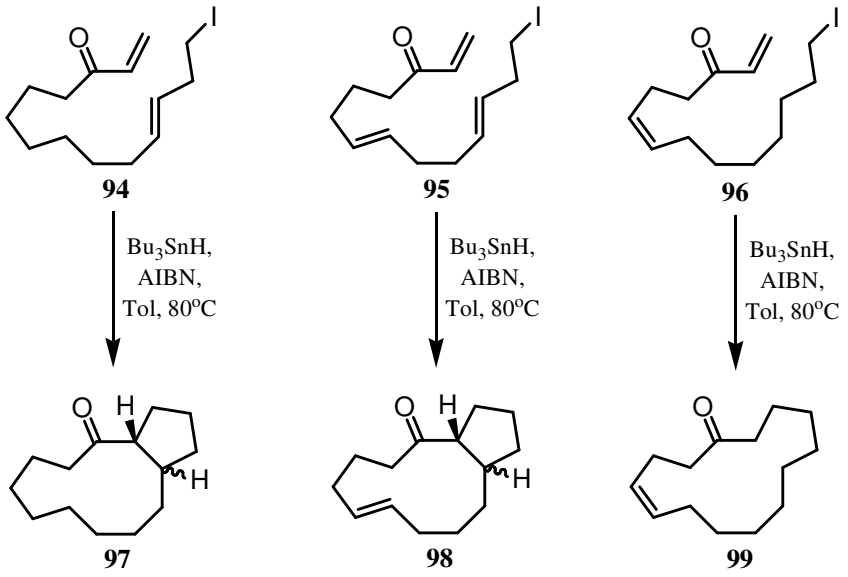
An enantioselective radical macrocyclisation has been developed by Porter *et al*., *via* the use of a chiral auxiliary attached to the electrophore. This was utilised in a synthesis of *R*-muscone **93**. Thus, when the olefin **91** (bearing a dimethylpyrrolidine amide) was treated with tributyltin hydride and AIBN, the major product formed was the macrocycle **92**. This system produced a 14:1 diastereomeric ratio in favour of the desired product **92** which was subsequently converted into *R*-muscone **93** (Scheme 18).[65]

A Radical-Mediated Macrocyclisation-Transannulation Cascade

Combining a radical macrocyclisation with the potential for subsequent cascading transannulations provides the opportunity for the elaboration of a complex polycyclic structure in a single step.

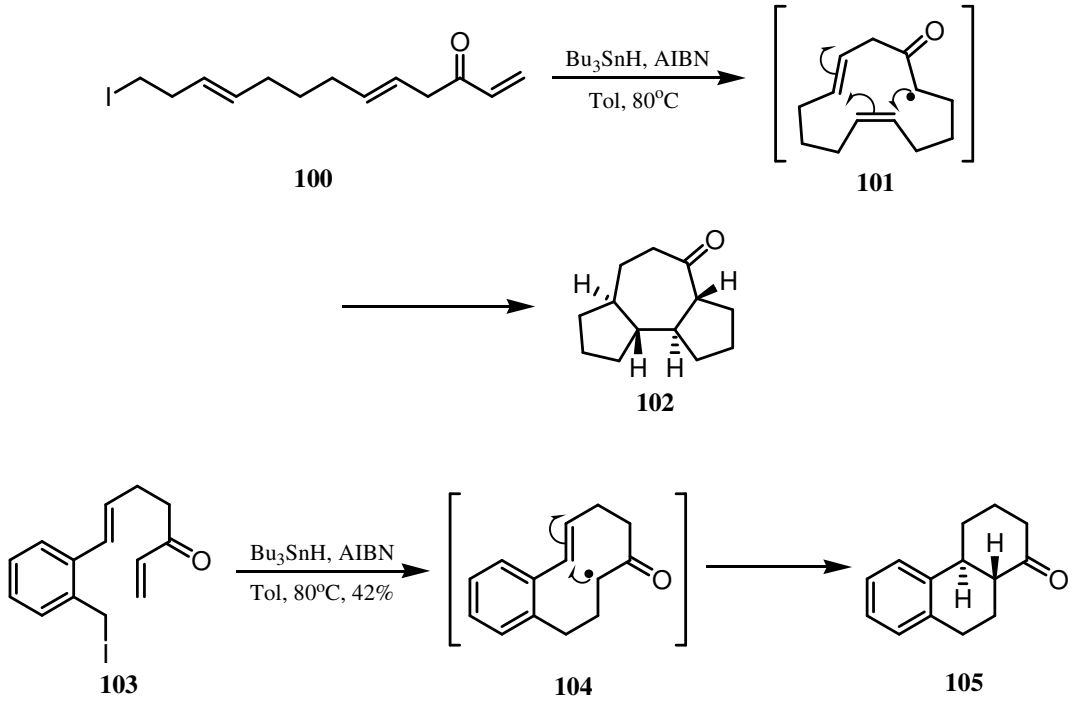
Some relatively straightforward examples from the laboratories of Porter demonstrate the delicate nature of these cascades. In the first example the iodide **94** underwent a 14-*endo*-trig radical macrocyclisation in the presence of tributyltin hydride and AIBN, in toluene at 80^{o}C. The resulting stabilized radical then underwent a 5-*exo*-trig transannulation leading to the bicycle **97**. In the second example the iodide **95** underwent a similar macrocyclisation-transannulation reaction sequence but **95** also has an extra olefin, positioned so that the bicyclic radical could undergo a second 5-*exo*-trig transannulation. However, this cascade did not continue further. Neither did the alkyl iodide **96**, in the third example, undergo the expected 5-*exo*-trig transannulation into the *Z*-alkene bond in **96**.[66] These examples serve to illustrate the subtle effects which can alter the outcome of these macrocyclisation-transannulation processes, and i) why careful prior planning

is required,[67] and ii) why more research is required in this area so that the processes can be more accurately predicted and controlled (Scheme 19).



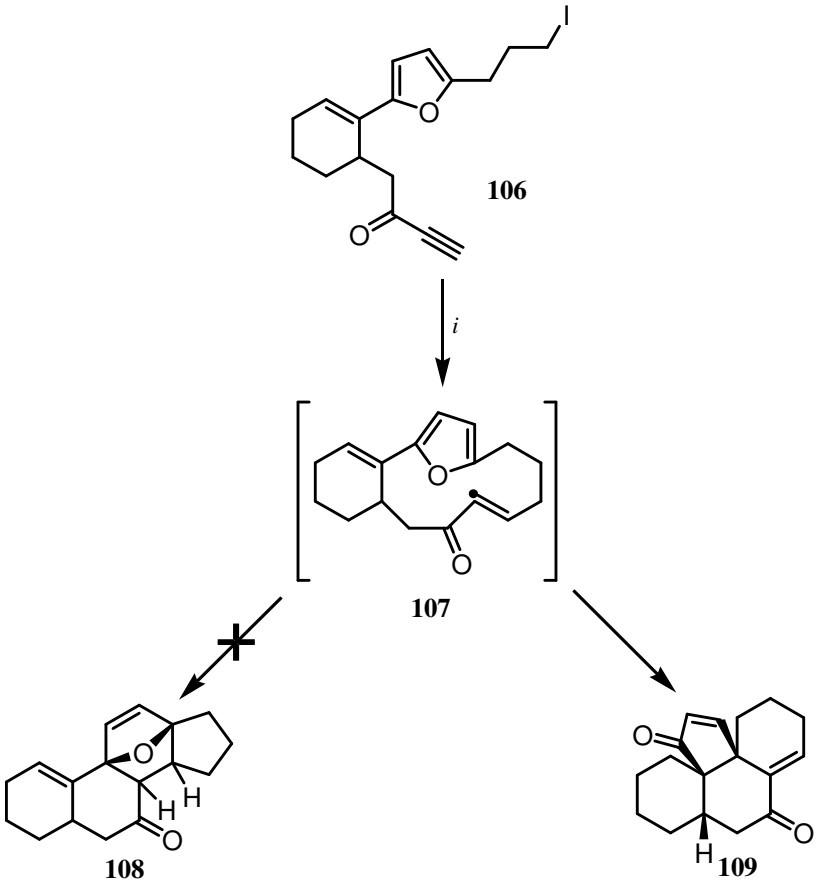
Scheme 19 Subtle conformational effects during a radical macrocyclisation-transannulation

Our own group in Nottingham has successfully demonstrated the elegance of this cascade strategy, converting various linear polyenes into polycyclic structures with a much higher level of complexity. I have chosen two examples from our early work which demonstrate this escalation in complexity during the radical cascade. In the first example the iodide **100** was smoothly converted into the tricycle **102** in 55% yield (its stereochemistry having been rationalized by MM2 molecular modeling studies).[68] The second example with the iodide **103**, successfully modeled the construction of the ABC rings of a ring-A aromatic steroid, such as estrone **21** (Scheme 20).[69]



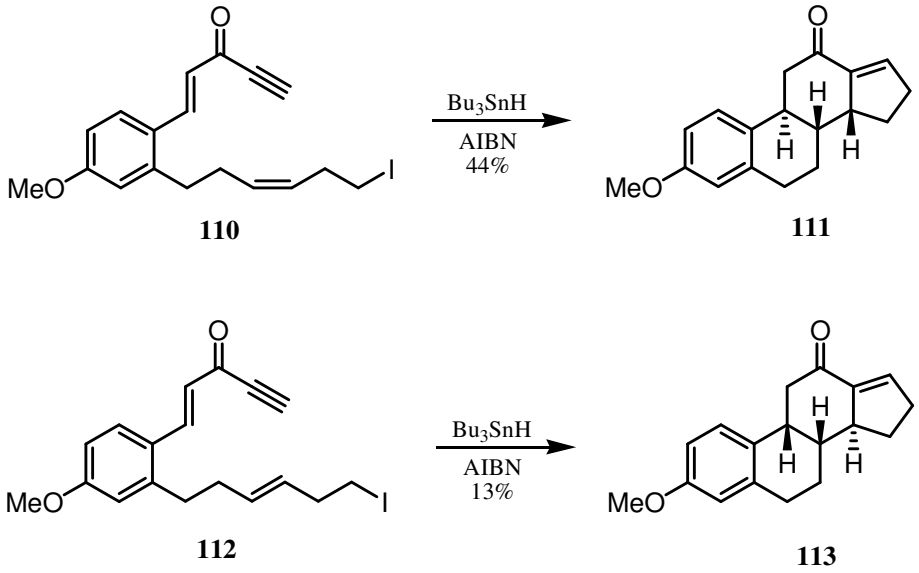
Scheme 20 Nottingham's early successes with radical macrocyclisation-transannulation cascades.

Our research group has also published some interesting results from attempted radical cascades which did not follow the desired plan but which provided exciting outcomes nonetheless and were worthy of note. For example, an attempt to synthesise the model steroid **108** from the simple iodoenynone **106**, instead resulted in the tetracyclic structure **109**. This was thought to be due to the intermediate radical **107** adding into the opposite side of the furan to that desired, which was then followed by an unexpected fragmentation. Such unexpected results underline the need for the careful consideration of all potential reactions of intermediate radicals and the subtle changes which can lead to such unexpected but interesting structures (Scheme 21).[70]



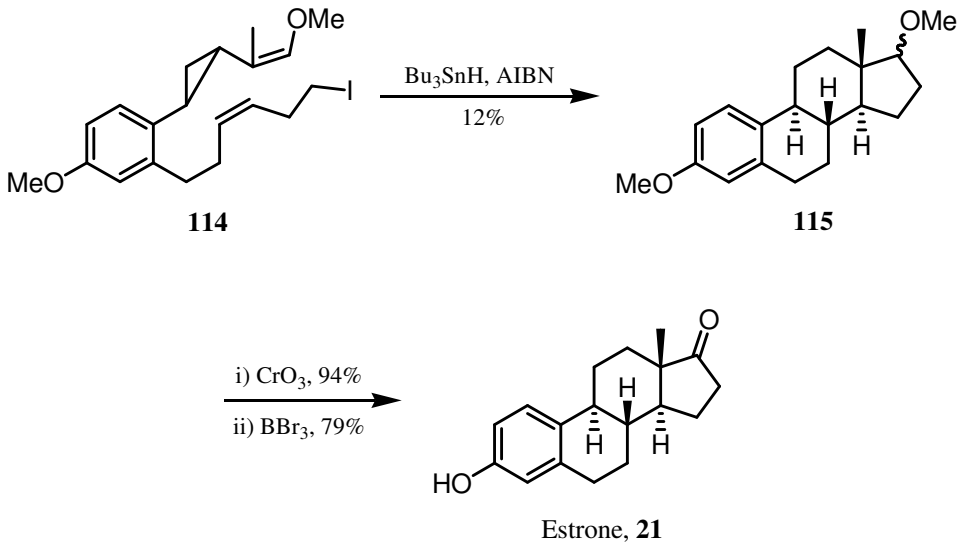
Scheme 21 *Reagents and conditions* i) Bu_3SnH, AIBN, benzene, 80°C, 2.5h, 40%.

The development of the strategy led our group to investigate approaches to the construction of the steroid skeleton *via* a radical macrocyclisation-transannulation cascade and the ring-A aromatic steroid estrone **21** was chosen as a suitably ambitious target. Initially two model systems were devised by our group to investigate a possible route towards estrone **21**. Thus, the *Z*- and *E*-iododienynones **110** and **112** were subjected separately to the radical generating conditions of tributyltin hydride and AIBN, and both underwent the expected 13-*endo*-dig radical macrocyclisation followed by the intended double transannulations. However, whilst these results were remarkable and justified continued studies, the desired steroidal stereochemistry was not achieved (Scheme 22).[71]



Scheme 22 Nottingham's model radical cascades towards estrone **21**.

These results, and others, led our group to take a different approach in the synthesis of estrone **21** *via* a radical cascade strategy, and instead to use a vinylcyclopropane as the electrophore. The successful total synthesis of estrone **21** was completed using the iodovinylcyclopropane precursor **114**.



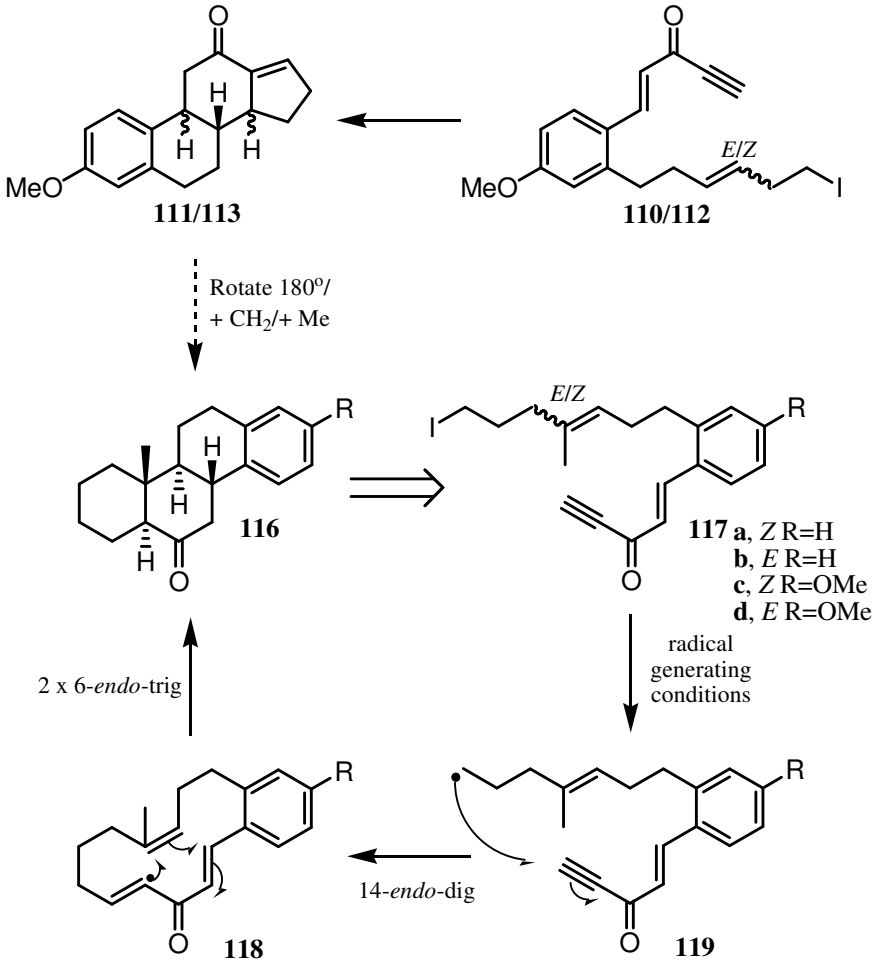
Scheme 23 A total synthesis of estrone **21** by a radical cascade.

The vinylcyclopropane **114** underwent the desired 13-*endo*-trig radical macrocyclisation and subsequent transannulations, to yield an advanced tetracyclic intermediate, this time with the correct steroidal stereochemistry. A further two steps (oxidation and deprotection of the phenol) led to an impressive cascade synthesis of estrone **21** (Scheme 23).[72]

Having successfully completed a total synthesis of estrone **21**, our group decided to test the aforementioned radical macrocyclisation-transannulation strategy on a yet more challenging target, *i.e*. the nicandrenones.

A Ring-D Aromatic Model System

It is at this point in time that the author joined the laboratories in Nottingham and to examine a radical cascade approach to the ring-D aromatic steroids. A model system would almost certainly be required initially and we decided upon a scheme which would use a strategy similar to that used for the related iodides **110/112**. However, the problem of the steroid stereochemistry still needed to be addressed and, after careful consideration, we decided upon the addition of an angular methyl group at the 10-position (the 14-position on **110/112**). Whilst this introduced a new risk, in that it set up three new protons susceptible to 1,5-hydrogen abstraction,[73] we believed it would also enforce the desired transition state and result in the desired *trans*, *anti*, *trans* steroid stereochemistry. Hence, synthetic routes to the model radical precursors **117a-d** were devised (Scheme 24).



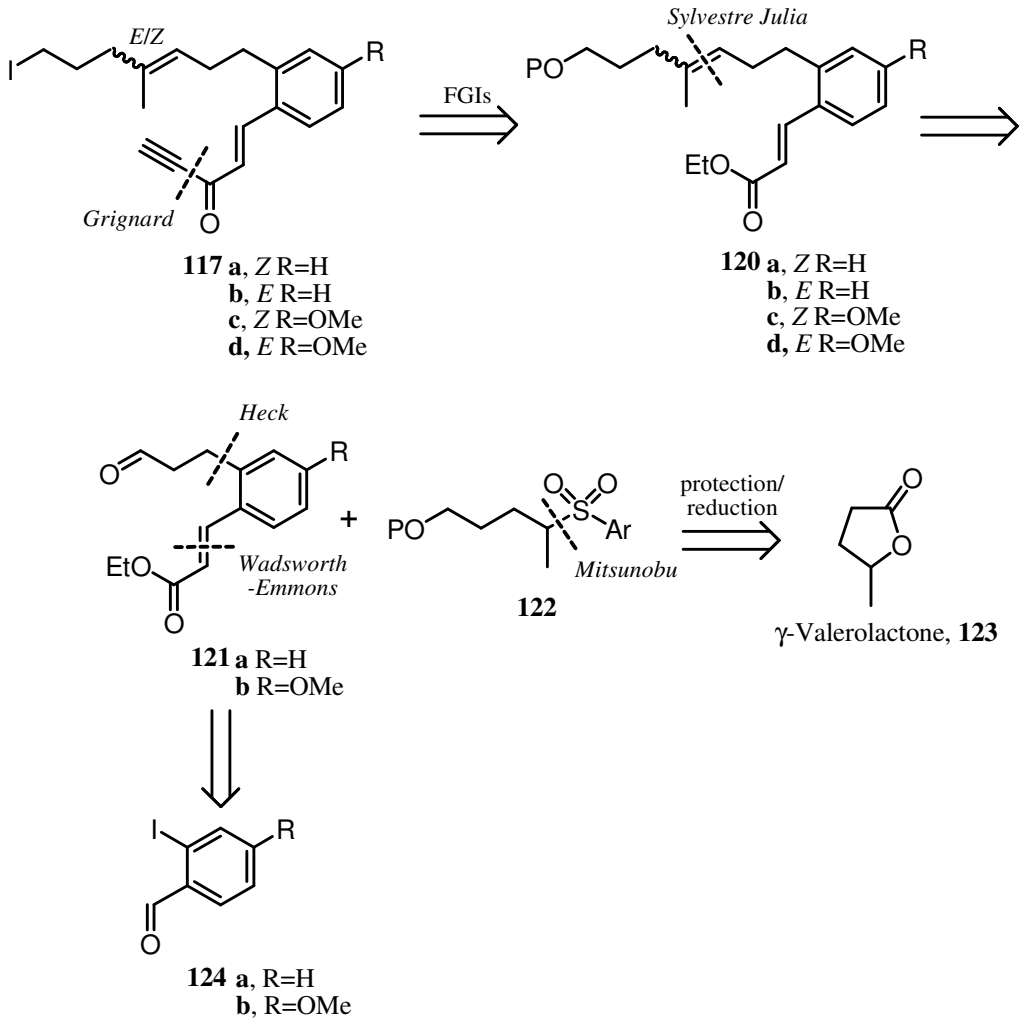
Scheme 24 Model system for the construction of a 6,6,6,6 ring-D aromatic steroid.

Upon generating the alkyl radical intermediate **119** we hoped that instead of the feared 1,5-hydrogen abstraction, the radical centre would undergo the desired 14-*endo*-trig radical macrocyclisation leading to the new vinyl radical **118**. This radical should then be held close enough to the remaining unsaturation in the macrocyclic trienone that the subsequent transannulations would occur smoothly resulting in the tetracycle **116** (Scheme 24).

We decided to synthesise the four different radical precursors (**117a-d**) *i.e. E*/*Z* analogues about the trisubstituted olefin (so as to test the stereochemical effect of this olefin on the stereochemistry of the final tetracycle) and also the methoxy and des-methoxy variants about the aromatic ring (this was to determine the effect on

the efficiency of the radical cascade of a methoxy substituent on the aromatic ring, which could also be used as a handle for attaching a side chain to the steroid at a later stage in the real system).

Firstly, we needed to synthesise **117a-d** as quickly, efficiently and as simply as possible. We therefore proceeded by disconnecting the lower ynone chain in **117** *via* a Grignard reaction,[74] (and three functional group interconversions) to provide us with the ester **120**.



Scheme 25 A retrosynthetic analysis of the radical cascade precursors **117a-d**

The upper iodo alkenyl chain in **117** could then be disconnected back to a protected alcohol (*via* a Finkelstein reaction[75] and deprotection) leading to the protected alcohol **120**. Having simplified the radical precursor **117** to the ester **120**, we next decided to make the synthesis more convergent and disconnect the trisubstituted olefin in **120** by means of a (Sylvestre) Julia olefination.[76,77] This we surmised, would allow access to both *E*- and *Z*-olefin isomers, and would lead us back to the known aldehydes **121a,b**[72] and the fairly straightforward looking sulfone **122**. The aldehydes **121a,b** would come from the 2-iodobenzaldehydes **124a,b**, of which both methoxy- and *des*-methoxy- variants are easily accessed, and the sulfone **122** could be synthesised from the widely available γ-valerolactone **123** in four relatively straightforward steps (Scheme 25).

This retrosynthesis was appealing for several reasons. Thus, the Julia disconnection ensured a convergent synthesis and allowed us to start from the known aldehydes **121a,b**,[72] and the remainder of the proposed reactions seemed uncomplicated and should be high yielding so as to ensure we achieved our goal as quickly as possible.

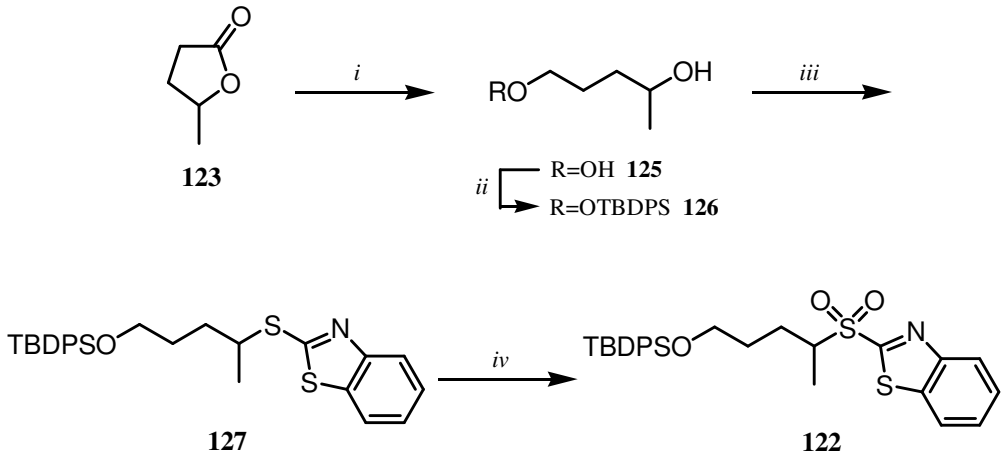
The first task was to synthesise the olefination coupling partners *i.e*. the sulfone **122** and the methoxy and *des*-methoxy aldehydes **121a,b**.

Syntheses of the Sulfone 122 and the Aldehydes 121a,b

The first step in the synthesis of the sulfone **122** was the selective protection of the primary alcohol group in 1,4-pentanediol **125**. However, whilst the diol **125** was available commercially, the quantity of compound required for the synthesis made the purchase of 1,4-pentanediol **125** commercially unviable. We therefore synthesized the diol **125** in large quantities from the available and inexpensive γ-

valerolactone **123**, *via* a lithium aluminium hydride reduction, in good yield.[78] Having obtained a sufficient quantity of the diol **125** we then selectively protected the primary alcohol group. We chose the *tert*-butyldiphenylsilyl (TBDPS) protecting group, and this performed well (initial test reactions with the less expensive *tert*-butyldimethylsilyl (TBS) protecting group demonstrated that this led to the compound becoming unstable during the later sulphide oxidation step), and proceeded in high yield with the trace amounts of *bis*-protected material being easily separated.

A Mitsunobu coupling[79] of the alcohol **126** was then chosen to introduce the aromatic sulphide component required for the Julia olefination. Past experience within our group had shown the benzothiazole to be superior to the Kocienski-modified Julia tetrazole, when used with a small secondary alcohol.

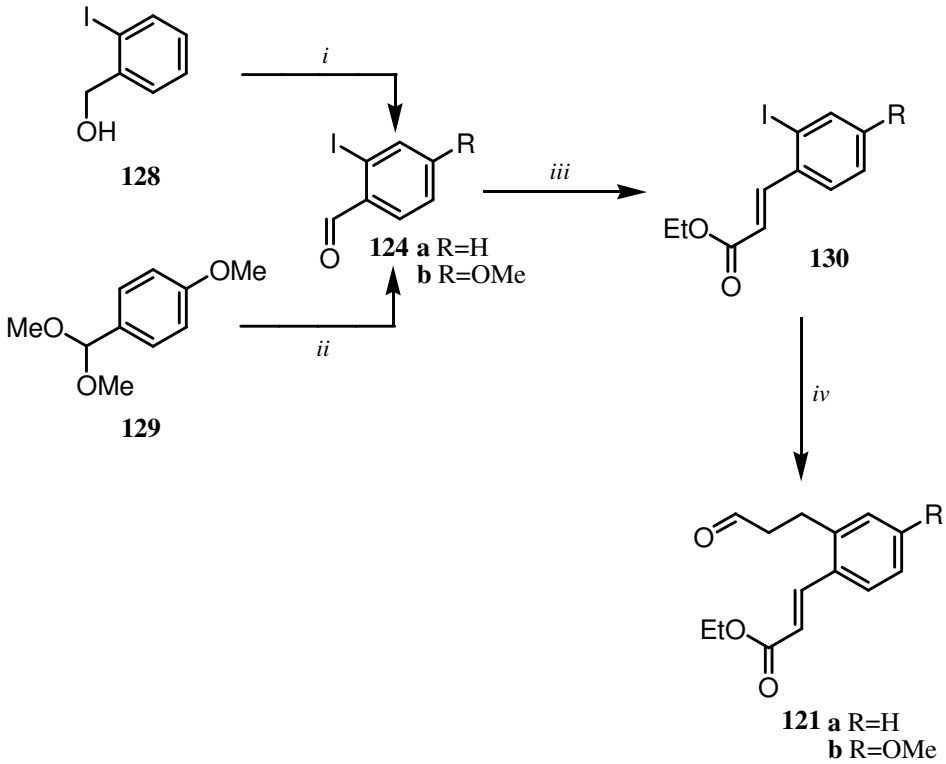


Scheme 26 *Reagents and conditions* i) $LiAlH_4$, THF, 0°C→r.t, 2h, 97%; ii) TBDPSCl, NaH, THF, 0°C, 2h, 98%; iii) 2-Mercaptobenzothiazole, PPh_3, DEAD, THF, 0°C→r.t, 24h, 99%; iv) *m*-CPBA, $NaHCO_3$, DCM, -40°C→0°C, 12h, 93%.

Utilising 2-mercaptobenzothiazole, the coupling reaction proceeded in high yield (when the DEAD reagent was used) and the employment of 3-chloroperbenzoic acid in the subsequent oxidation step also ensured a good yield on both test and

larger scales. This completed a simple and efficient large scale synthesis of the sulfone **122** (Scheme 26).

The two substituted aldehydes **121a,b**, required for the Julia coupling with the sulfone **122**, were known compounds from earlier work within our research group. However, Scheme 27 shows the yields and the conditions used by us in large scale syntheses of these key intermediates.

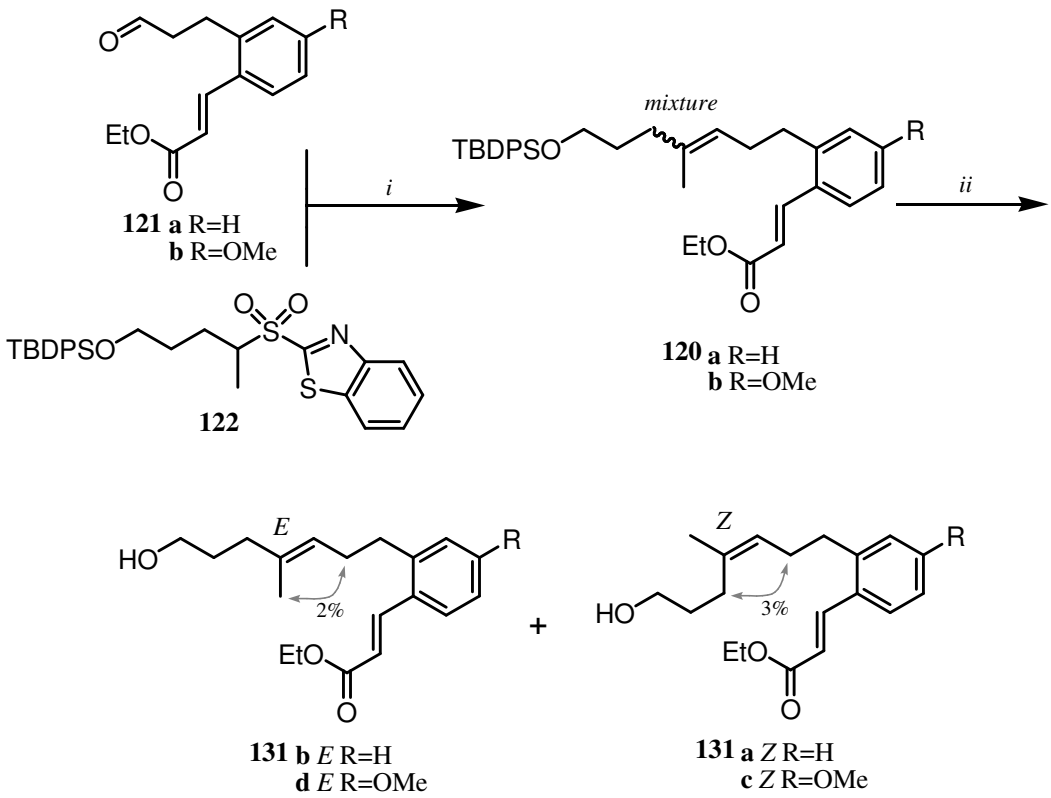


Scheme 27 *Reagents and conditions* i) MnO_2, DCM, r.t, 24h, 94%; ii) a) ^tBuLi, Et_2O, -78°C→r.t, 3h, b) I_2, -78°C→r.t, 84%; iii) Triethylphosphono acetate, NaH, THF, 0°C→r.t, 24h, R=H: 81%, R=OMe: 87%; iv) $Pd(OAc)_2$, Allyl alcohol, Bu_4NCl, $NaHCO_3$, DMF, 40°C, 5h, R=H: 84%, R=OMe: 95%.

Having prepared sufficient quantities of the coupling partners **121a,b** and **122**, we now examined the planned Julia olefination reactions, and the completion of the syntheses of the radical precursors **117a-d**.

Syntheses of the Iododienynones 117a-d

Our initial attempts at coupling the aldehydes **121a-b** with the sulfone **122** were successful, but they gave lower yields than expected. Since this was a key step in our synthesis we decided to conduct an extensive optimisation study. However, our attempts to improve the yield by trying different bases (NaHMDS, LiHMDS, KHMDS), altering the amount of base (1.1eq, 1.2eq, 1.5eq), changing the solvent (THF, DME), temperature of addition (-78°C, -50°C), and type/order of addition failed to improve the yields significantly (*i.e.* optimised yields of 38-55%). We postulated that the lower than expected yield in this coupling were perhaps due to a low nucleophilicity of the sulfone anion.

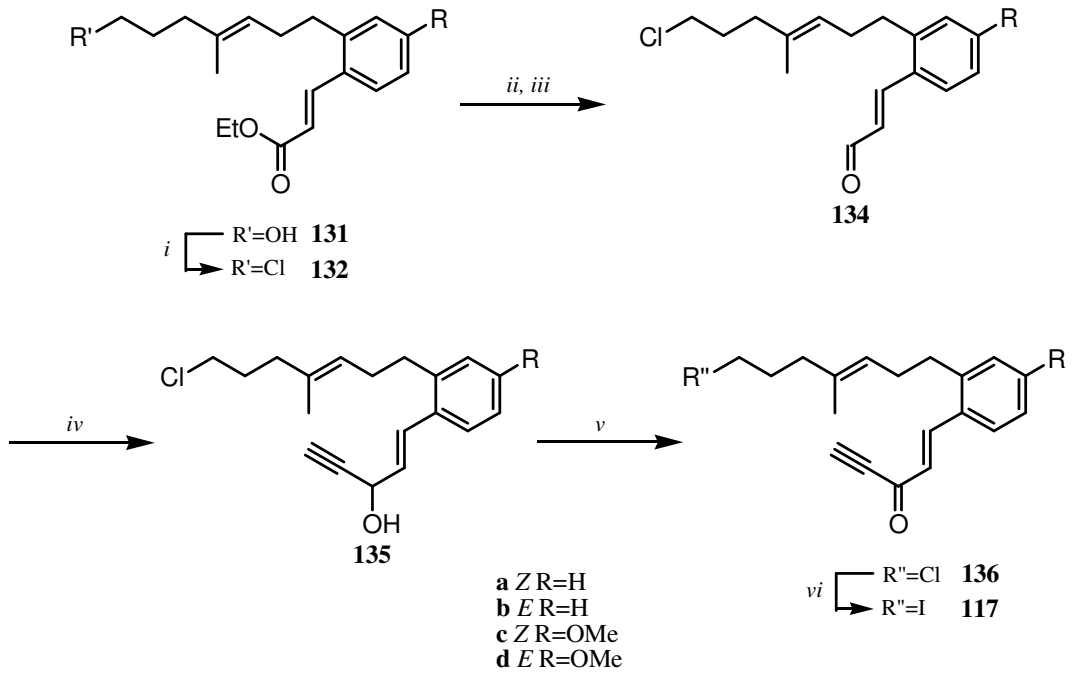


Scheme 28 *Reagents and conditions* i) NaHMDS, THF, -78°C, 14h, R=H: 38%, R=OMe: 55%; ii) TBAF, THF, 0°C→r.t, 3h, R=H(*Z*): 25%, R=H(*E*): 52%, R=OMe(*Z*): 32%, R=OMe(*E*): 37%.

The olefination reactions led to inseparable mixtures of olefin isomers **120a,b**, in 3:2 ratios in favour of the *E*-trisubstituted double bond. Taking, separately, both the methoxy and *des*-methoxy mixtures, we next deprotected the *tert*-butyldiphenylsilyl groups using TBAF reagent at 0^{o}C. These deprotections proceeded in high yields, and allowed us (with the aid of careful flash column chromatography) to separate each of the *Z* and *E*-isomers of the resulting alcohols thereby allowing us to continue the syntheses with pure *Z*- **131a,c** and pure *E*-alkenes **131b,d** (the alkene stereochemistry was confirmed by n.o.e) (Scheme 28).

We now proceeded to convert each alcohol into the iododienynones **117a-d**. We first chlorinated the alcohols using freshly recrystallised *N*-chlorosuccinimide and triphenylphosphine yielding the chlorides **132a-d** in good yield.

In order to prepare the enynone portions in the targets, we first reduced the ethyl esters **132a-d** to the corresponding alcohols **133a-d** using diisobutylaluminium hydride which were then oxidised to the aldehydes **134a-d** using manganese (IV) oxide. This procedure went smoothly and in excellent overall yield. Addition of ethynylmagnesium bromide to the aldehydes **134a-d** next led to the allylic alcohols **135a-d** which were oxidised to the corresponding ketones **136a-d** using manganese (IV) oxide. These oxidations proved to be problematic and clean ynones were only obtained in very low yield, until vigorous and successive washings of the filter cake with dichloromethane and hot ethyl acetate were performed. We postulated that the 'triply' enynones were strongly 'adhering' to the active sites of the manganese (IV) oxide. The chloroenynones **136a-d** were stable, and could be stored easily until the much less stable iododienynones **117a-d** were needed. These were prepared by a simple Finkelstein reaction with sodium iodide in good yield (Scheme 29).



Scheme 29 *Reagents and conditions* i) NCS, PPh_3, K_2CO_3, DCM, 0°C→r.t, 1h, R=H(*Z*): 96%, R=H(*E*): 98%, R=OMe(*Z*): 90%, R=OMe(*E*): 91%; ii) DIBAL-H, DCM, -78°C, 3h, R=H(*Z*): 86%, R=H(*E*): 85%, R=OMe(*Z*): 92%, R=OMe(*E*): 87%; iii) MnO_2, DCM, r.t, 21h, R=H(*Z*): 89%, R=H(*E*): 87%, R=OMe(*Z*): 81%, R=OMe(*E*): 81%; iv) Ethynylmagnesium bromide, THF, -78°C→r.t, 20h, R=H(*Z*): 98%, R=H(*E*): 98%, R=OMe(*Z*): 99%, R=OMe(*E*): 93%; v) MnO_2, DCM, r.t, 18h, R=H(*Z*): 81%, R=H(*E*): 86%, R=OMe(*Z*): 86%, R=OMe(*E*): 88%; vi) NaI, K_2CO_3, 2-butanone, 80°C, 23h, R=H(*Z*): 87%, R=H(*E*): 88%, R=OMe(*Z*): 92%, R=OMe(*E*): 95%.

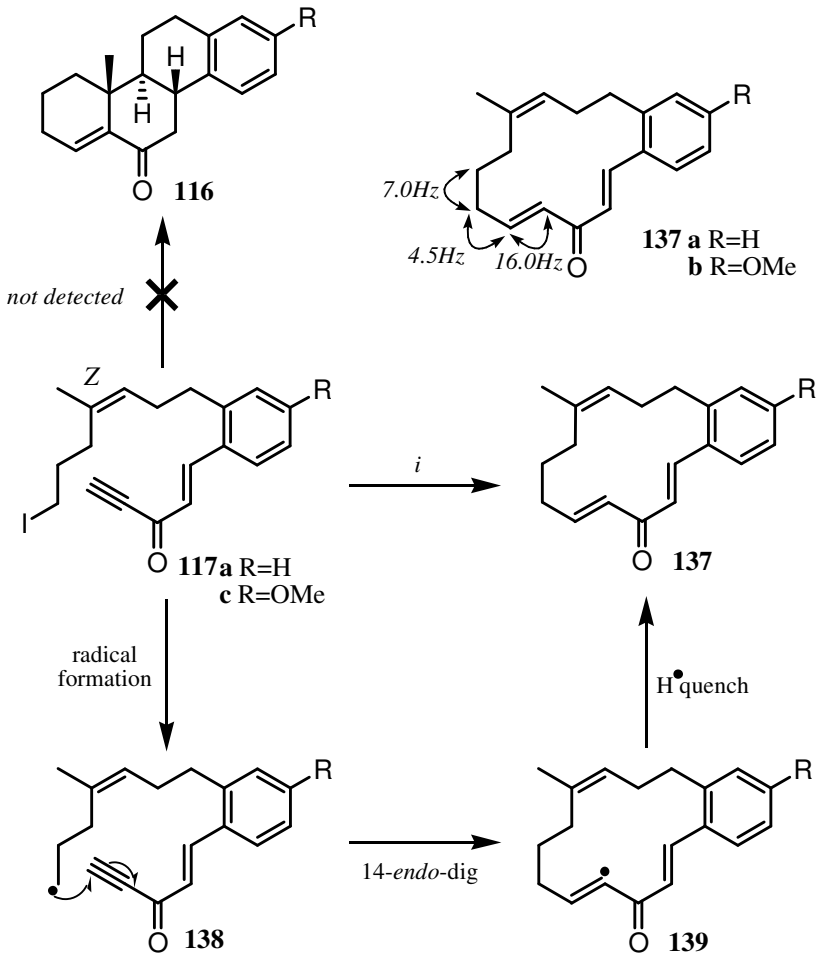
With reasonable quantities of all of the four radical precursors **117a-d** in hand, we now turned our attention to investigating the radical cascade processes.

The Proposed Radical Cascades from the Precursors 117a-d

The Radical Cascades from the *Z*-Iododienynones 117a,c

Our attempts to produce a 6,6,6,6 ring-D aromatic steroid, by subjecting the *Z*-radical precursors **117a** and **117c** to the standard radical generating protocol of tributyltin hydride and AIBN, were initially unsuccessful. Numerous different conditions were tried but we shall concentrate here on the exciting results eventually obtained from this radical cascade.

Conditions were found which resulted in a single identifiable product from **117a** and **117c**. This particular system was more sensitive than other more standard radical precursors that the author has worked on and there were several noteworthy modifications required in order to achieve the conversion of the *Z*-iododienynones **117a,c** into their cascade products **137a,b**. Most notable was the need for more extensive degassing of the solutions than was normally required, and the need for the reagents and substrates to be more rigorously dried than was normal. The single product isolated from the cascade mixture (in 36% yield) was analysed and it was rapidly discovered that it was not the desired 6,6,6,6 ring-D aromatic steroid **116a,c**.



Scheme 30 *Reagents and conditions* i) Bu_3SnH, AIBN, benzene, 80°C, 20h, *R=H*: 35%, *R=OMe*: 36%.

Analysis of the proton and carbon NMR spectroscopic data showed that the cascade product had retained the aryl enone and trisubstituted olefin units, but had lost the alkyne signals to be replaced by two new olefin proton signals. Analysis of the 2D NMR spectra demonstrated coupling from the new olefin proton signals around a three carbon chain to the trisubstituted olefin. These, and other, spectroscopic data, led us to propose the macrocyclic structures **137a,b** for the radical cascade products of the *Z*-iododienynones **117a,c**. We postulated that these structures result from the 14-*endo*-dig radical macrocyclisation of the alkyl radical **138** and the subsequent quenching of the intermediate vinyl radical **139** before any transannulation reaction could occur (Scheme 30).

That the required 14-*endo*-dig radical macrocyclisation should have occurred, but the subsequent transannulations did not take place seemed strange to us initially, especially considering our past experiences with related substances (see **110/112**). However, upon further consideration we postulate that the fourteen membered macrocyclic radical **139** with the *Z*-trisubstituted olefin is held in a very 'open' conformation and that the distance between the carbon-centered radical in **139** and the trisubstituted olefin (in the lowest energy conformation), is simply too great to overcome (calculated as 5.27Å).

This result led us to examine some molecular mechanics calculations (with the assistance of Prof. B. Lygo) on the radical macrocycles **137a,b**. These calculations demonstrated that the energy difference between the least energy conformation of the *Z*-macrocycle **142** and the conformation required for the desired transannulation bond formation to occur **140** (and by loose inference a general approximation of the energy barrier that must be overcome), is approximately four times that

required for the *E*-macrocycle to undergo transannulation. These data gave credence to our assigned macrocyclic structure **137** and provided hope that the *E*-precursors **117b,d** would not suffer the same problem/outcome (Figure 2).

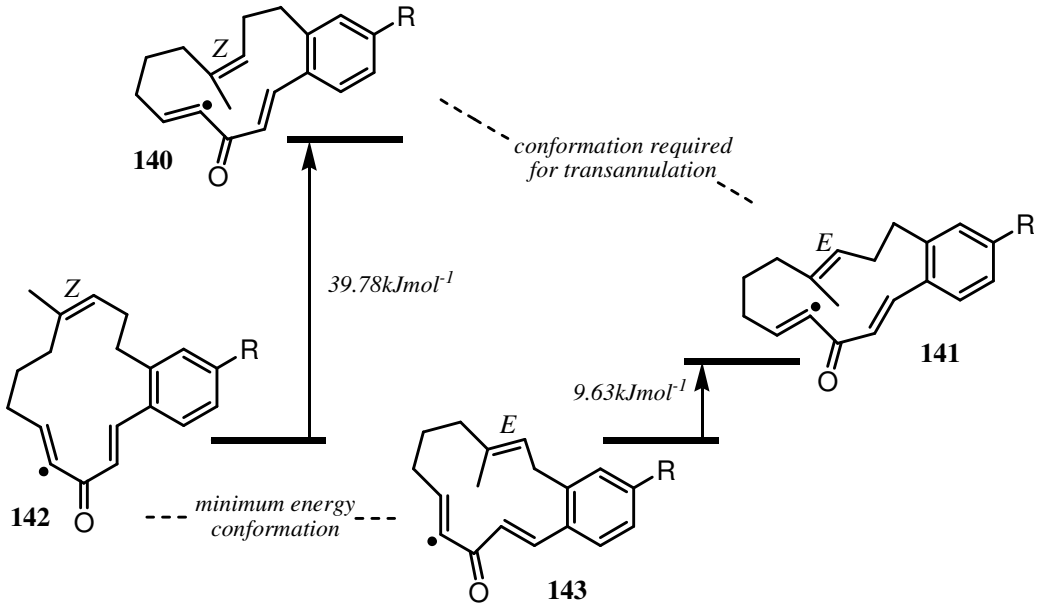
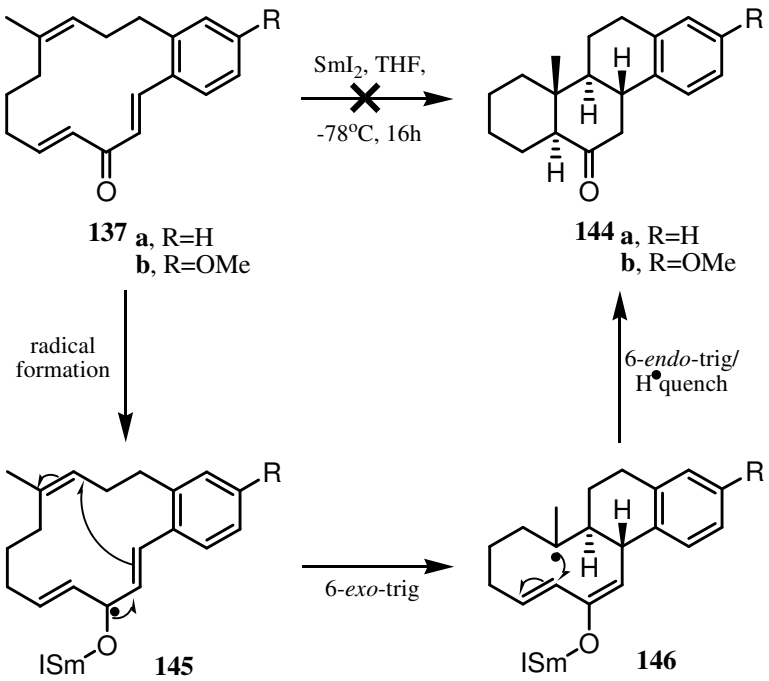


Figure 2 Computational energies of the macrocyclic radicals **140** - **143**.

Having failed to produce the anticipated tetracycle **116** from the *Z*-precursors **117a,c**, we decided to attempt to 'force' the transannulations in the *Z*-macrocycles **137a,b**. This endeavor was undertaken by treating the macrocycles **137a,b** with samarium diiodide. We hoped that this would produce the ketyl radical which would subsequently induce the desired transannulations, albeit as a separate cascade (Scheme 31).



Scheme 31 A proposed conversion of the macrocycle **137** into the tetracycle **144**.

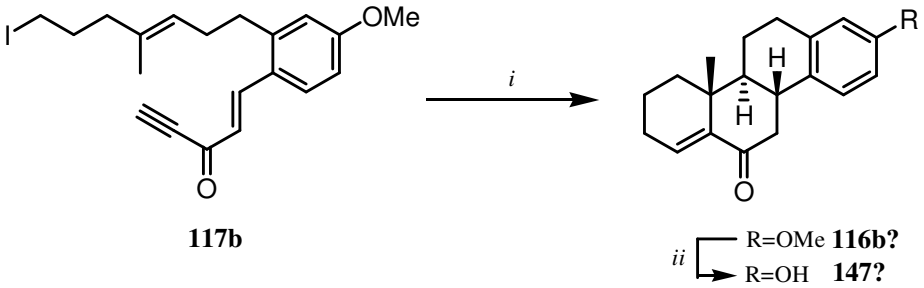
Unfortunately, we were unable to isolate any tetracyclic structures **144a-b** from the reaction. Nevertheless, we were still hopeful that the corresponding *E*-radical precursors **117b,d** would undergo transannulation successfully.

The Radical Cascades from the *E*-Iododienynones 117b,d

Taking the *E*-radical precursors **117b,d** we subjected them to the radical generating conditions of tributyltin hydride and AIBN, in refluxing benzene. A single product was isolated as a yellow oil in each case, in a respectable yield of 35%. As before the radical cascade was unusually sensitive and we discovered that a greater than the usual catalytic amount of AIBN initiator was required in order to produce this product (approximately 0.3eq instead of the normal 0.01-0.1eq). Analysis of the spectroscopic data for the products revealed the loss of the olefinic signals and the appearance of numerous new complex methylene signals in the aliphatic region of the proton NMR spectra. The spectroscopic data also revealed that the product was

present as a 2:1 mixture of diastereoisomers. Our initial assignments led us to believe that the spectra could indeed be produced by our desired tetracyclic ring-D aromatic steroid **116a,b**. However, there were some anomalous data (an unusually high integration of the aromatic protons and some anomalous carbon resonances) which cast doubts on our tentative structural assignment.

At this stage we decided that more 'absolute' evidence would be required to prove the structures of the cascade products from **117b,d** and thus we attempted to obtain a crystalline derivative of the cascade product, suitable for X-ray analysis. After careful consideration we decided that deprotecting the methoxy analogue **117b** to a phenoxy compound would be the most promising route to a crystalline derivative. Hence, we treated the cascade product **116b?** with boron tribromide (Scheme 32).



117b

Scheme 32 *Reagents and conditions* i) Bu_3SnH, AIBN, benzene, 80°C, 20h, *R=H*: 35%, *R=OMe*: 30%; ii) BBr_3, DCM, -78°C, 16h, 48%.

This product was indeed crystalline, and a successful X-ray crystal analysis was performed. To our surprise, the X-ray crystal structure (Figure 3) showed that the product we had produced was not the desired phenolic tetracycle **147?** but instead the unusual angular 6,6,6-ring fused substituted aromatic structure **147**. The structure was found to be the major isomer of **147** which had crystallised out separately from the minor isomer. An analysis of the spectroscopic data now

revealed that this structure was a much better fit for the NMR data obtained than the desired tetracycle **147?** (the unusually high integration of the aromatic protons and anomalous carbon resonances were due to the inclusion of a second aryl ring into the cascade product).

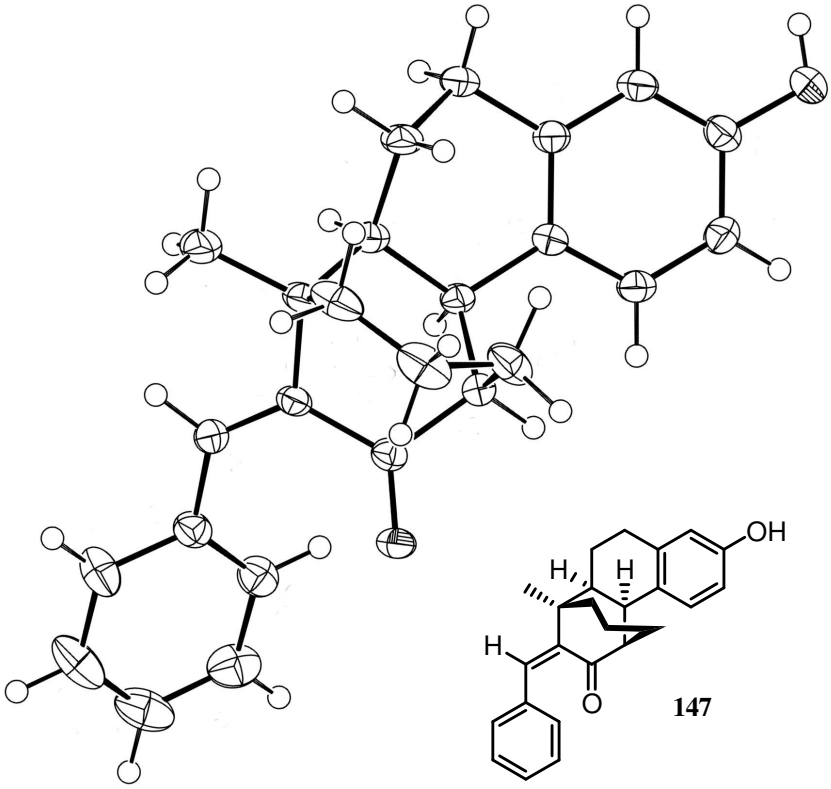
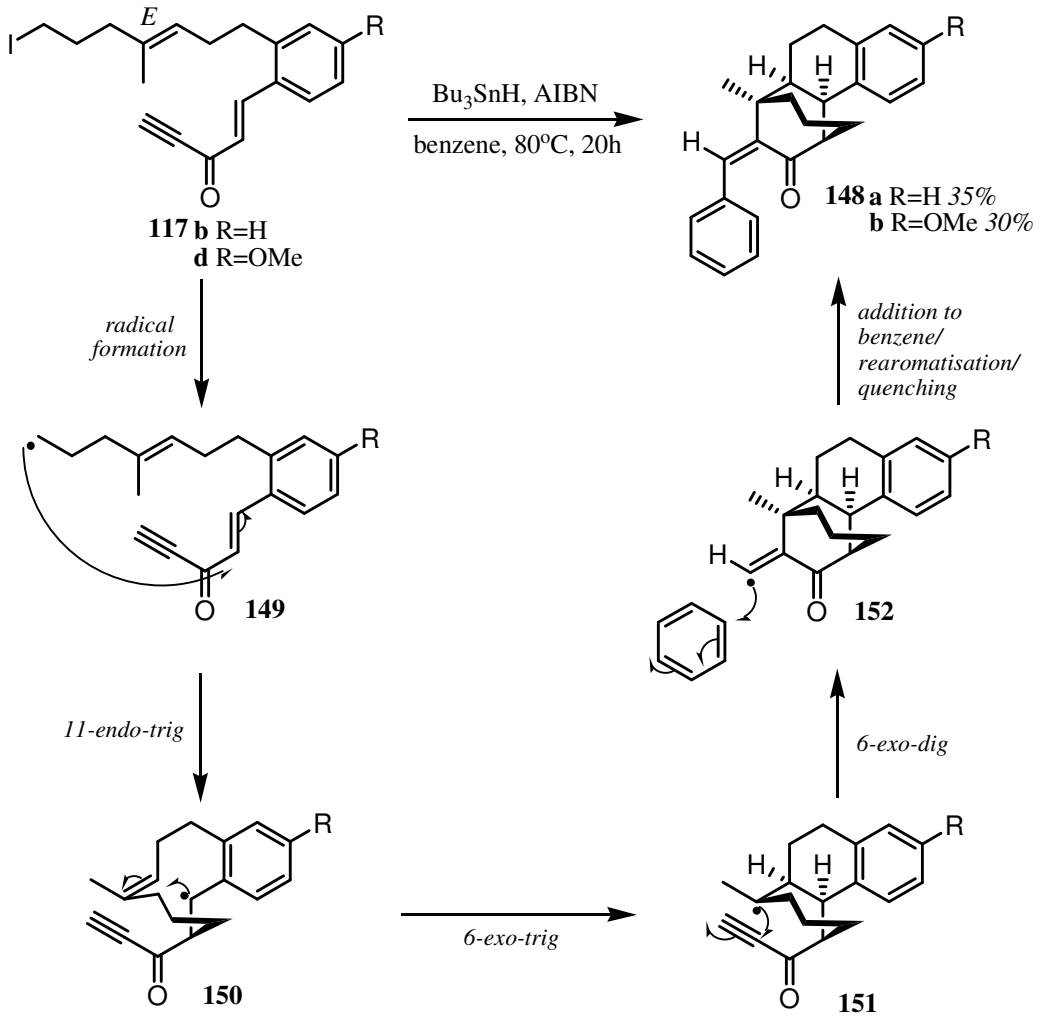


Figure 3 X-ray crystal structure analysis of the phenol **147**

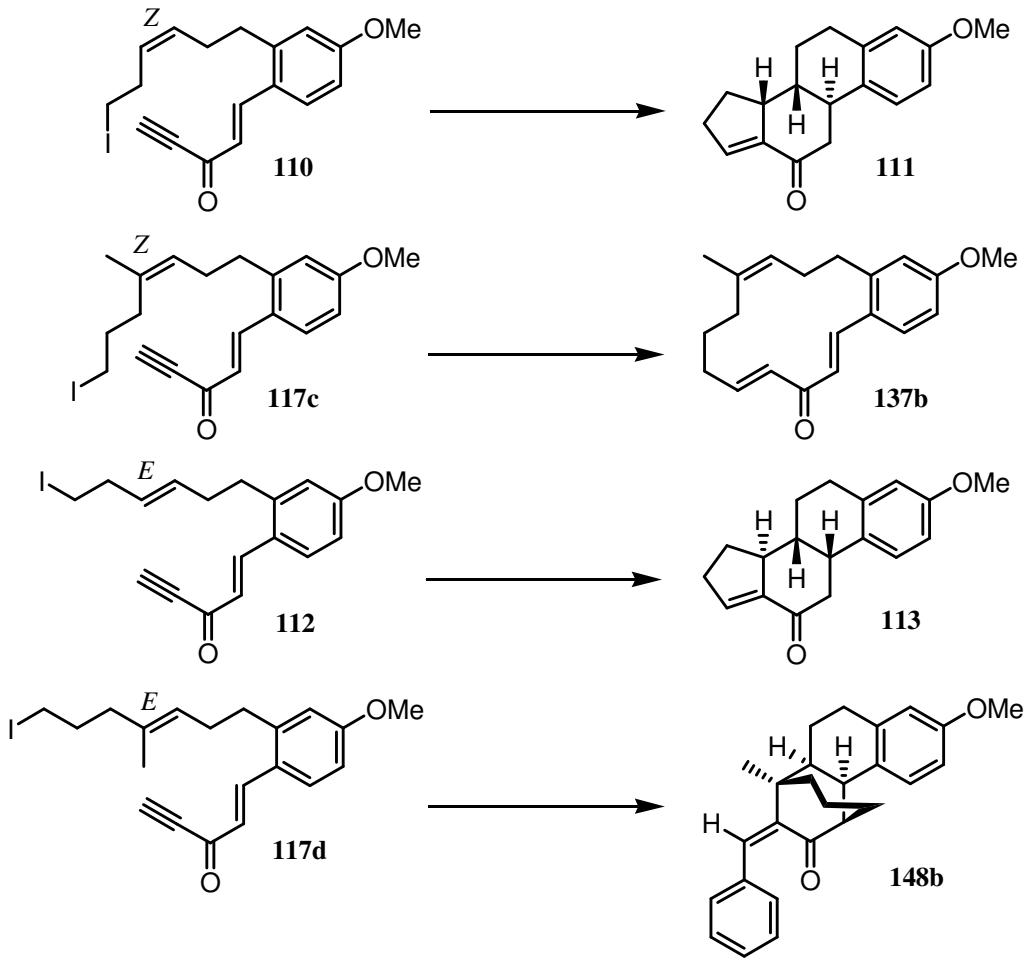
The formation of the unusual bridged tricycles **148a,b** requires three intramolecular carbon-to-carbon bond forming processes and an intermolecular radical coupling, presumably with the solvent benzene.



Scheme 33 A proposed mechanism for the synthesis of the bridged tricycle **148** from the *E*-iododienynone **117**

Having carried out a number of model reactions designed to probe the mechanistic possibilities for this unusual product outcome and performed an in-depth literature search, we postulate that the bridged tricycles **148a,b** are produced from the precursors **117b,d** by an initial 11-*endo*-trig cyclisation of the first formed radical **68**, leading firstly to the benzylic radical intermediate **150**. Sequential 6-*exo*-trig (to intermediate **151**) and 6-*exo*-dig radical cyclisations next lead to the vinyl radical intermediate **152**. The vinyl radical **152** is then quenched by the solvent benzene[80] resulting in the major and minor diastereoisomers of the benzylidene substituted tricycle **148** (Scheme 33).

In order to appreciate the remarkable outcome of these radical cascades we need to consider the results in comparison with those of the iododienynones **110/112**. Scheme 34 shows the radical cascades side by side.



Scheme 34 A comparison of the outcomes of the present radical cascades compared to others discovered in Nottingham.

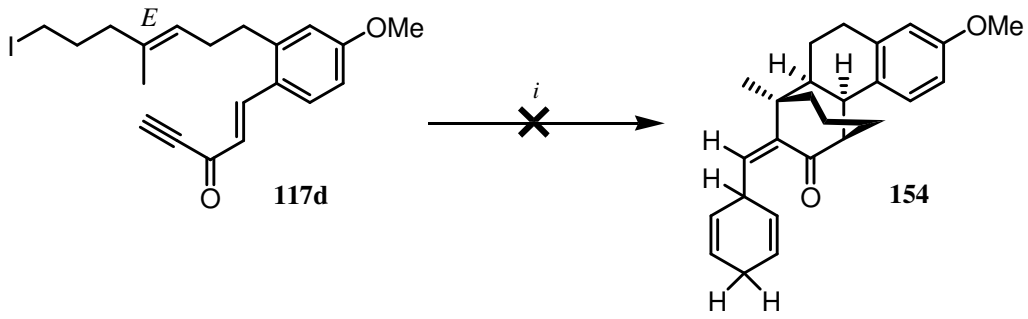
By synthesising **117** with an extra methylene in the iodo chain, and a tri- instead of di-substituted olefin, we see remarkably different product outcomes. The *Z*-isomers **117a,c** instead of constructing the tetracycle **116** alternatively halt at the macrocyclisation stage (probably due to new methyl group holding the macrocycle in a more 'open' conformation, as discussed in the preceding section). The *E*-

isomers **117b,d** instead of constructing the tetracycle **116** alternatively produce the unique bridged tricycle **148**.

We next set about attempting to resolve the route taken from the precursors **117b,d** during the radical cascade, which resulted in the bridged tricyclic structures **148a,b**. Taking *β*–bromostyrene in benzene, we attempted to 'replicate' the addition of a vinylic radical to benzene[81] under the same radical generating conditions. However, only styrene was isolated. An analysis of the literature concerning the aspects of these unusual radical cascades and the surprising outcome revealed several possibilities. In particular we were interested in the unusual way in which the cascade had seemingly terminated, *i.e*. by quenching of the postulated vinylic radical **152** on the solvent benzene and its subsequent rearomatisation to give **148a,b**. The process by which 1,4-cyclohexadienyl radicals aromatise appears to be contested in the literature with various and contradictory theories. However several papers, most notably those by the Crich[82] and Beckwith[83] groups, suggest that the initiator AIBN can act as the oxidant. We found that it was common in many[84,85] (but not all)[86] of the radical reactions involving addition to benzene-like systems, that "large amounts of initiator" were required.[87] This fits in with the requirement for more than the typical amount of initiator being necessary, for the successful synthesis of the benzene addition products **148a,b**. We postulate that the 'extra' AIBN required, beyond that needed to sustain the catalytic tin radical cycle, is used to oxidise/rearomatise the cyclodienyl radical and produce the bridged tricycle **148**.

In an attempt to prove this hypothesis we attempted to trap this postulated 1,4-cyclohexadienyl radical by utilising diphenyl diselenide to produce phenyl selenol *in situ*. This would provide the cyclohexadienyl radical with another source from

which to quench. We therefore treated the iodide **117d** under the same radical generating conditions that led to the formation of the benzene addition product **148b** with the following modifications: i) 0.2eq of diphenyl diselenide was added and ii) only 0.1eq of AIBN was added. We hoped this would result in formation of the 1,4-cyclohexadiene product **154**. Unfortunately, only starting iodide was recovered (Scheme 35).

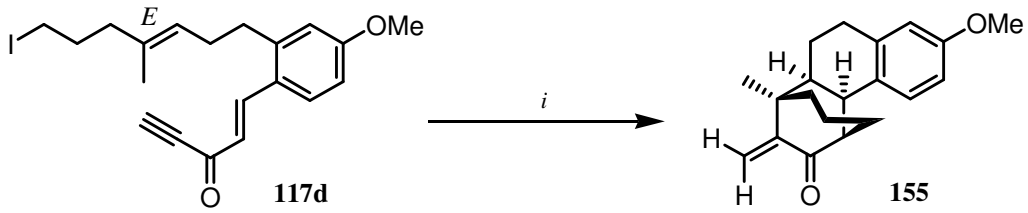


Scheme 35 *Reagents and conditions* i) Bu_3SnH, AIBN, $(PhSe)_2$, benzene, 80°C, 20h.

Numerous attempts were made, following these interesting results, to produce the desired tetracycle **116** by modifying the radical cascade reaction conditions. For example, the unusual postulated quenching by the solvent benzene, could suggest that the concentration of the tributyltin hydride is so low that the final 1,4-cyclohexadienyl radical intermediate quenches on benzene instead. We therefore increased the amount of tributyltin hydride hoping that the vinylic radical **152** would quench *via* hydrogen abstraction (or possibly the entire reaction pathway could be altered). However, a threefold increase in the concentration of tributyltin hydride had no effect, the only isolated product being the bridged tricycle **148**. Shortening the addition period of the tributyltin hydride to one hour unfortunately also yielded the same result. We also carried out the radical cascade of **117** using

TTMSS, as an alternative radical generator. This however, gave the same product and in a comparable yield.

In a parallel attempt to alter the quenching process and lend some credence to our proposed mechanism, we carried out the radical cascade of **117d** under the same tributyltin hydride radical generating conditions, but the reaction was carried out in *n*-heptane. We reasoned that without the benzene to react with/quench on, the postulated vinylic radical **152** would have to seek out another source or alternatively alter the reaction pathway. From this reaction mixture we isolated a subtly different product. The proton NMR showed this new product to be similar in many regards to the bridged tricycle **148b**. However there were less aromatic signals and two new signals at δ6.23ppm (1H, d, J 1.5Hz) and δ5.43ppm (1H, d, J 1.5Hz). These data suggested that the new product is the result of hydrogen quenching and is the methylidene substituted tricycle **155** (Scheme 36).



Scheme 36 *Reagents and conditions* i) Bu_3SnH, AIBN, heptane, 90°C, 20h, 18%.

These results, whilst interesting in themselves, become even more so when compared to the results of the radical cascades of the iododienynones **110** and **112** (see Scheme 34). Whilst the extra methylene and substitution on the alkyl olefin could feasibly alter the conformation of the *Z*-macrocyclic radical **139**, to the extent that it is unfavourable for it to transannulate as the iododienynone **110** does, we find it fascinating that these two subtle modifications can have such a dramatic

effect on the outcome of the *E*-radical precursors **117b,d**, completely altering the site of initial attack (cinnamyl *vs* ynone) and producing a structure which finds it more favourable to 'quench' on the solvent benzene, than the tributyltin hydride. We can only postulate that the extra methylene has allowed the upper alkenyl chain the length and conformational freedom, to reach the cinnamyl electrophore and so pursue a reaction route which was unavailable to the shorter iododienynone **112**.

In conclusion, we have evaluated the scope for a radical cascade reaction of an ynone electrophore towards synthesising a 6,6,6,6 ring-D aromatic steroid. Treatment of the *Z*-iododienynones **117a,c** with tributyltin hydride and AIBN led to the macrocycles **137a,b**, whilst treatment of the *E*-iododienynones **117b,d** gave the novel bridged tricycles **148a,b** and **94** (depending on whether benzene or heptane was used as the solvent), instead of the desired ring-D tetracycle **116**. Not for the first time these studies have demonstrated how interesting and yet how subtly unpredictable some radical reactions can be. This appears to be even more so when the radical intermediates are presented with numerous possibilities within a conformationally constrained environment, and yet these reactions have produced novel and interesting structures not available by more conventional synthetic methods.

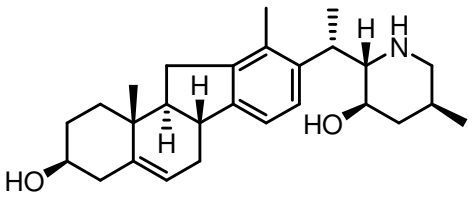
Results and Discussion

Part 2

A Cascade Radical-Mediated Approach

towards Veratramine

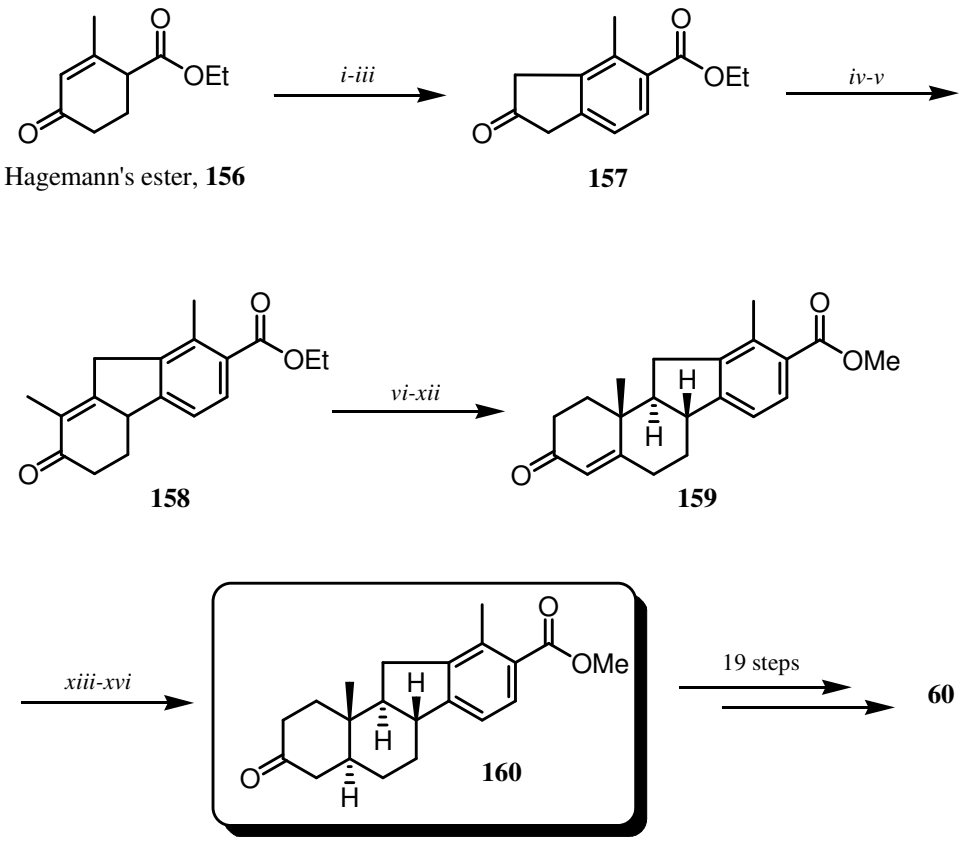
One of the better known natural products containing a 6,6,5,6 ring-D aromatic steroid ring system is the alkaloid veratramine **60**, and this compound was selected as a synthetic target for our research. Veratramine **60** was isolated from the white hellebore (*Veratrum grandiflorum*) by Saito *et al*. in 1940[44] and it exhibits interesting and potentially useful biological activity (see page 21).[45-48] There have been only two total syntheses of this interesting alkaloid. Kutney *et al*. published a synthesis of veratramine (and the structurally related 6,6,5,6 ring-D aromatic steroid known as verarine) in 1975,[88] following a total synthesis of veratramine **60** by Johnson *et al*. in 1967.[89]



Veratramine, **60**

W. S. Johnson and co-workers designed an annulation strategy towards **60**, constructing the steroid ring system one ring at a time, before attaching and modifying the alkaloidal side-chain. Thus, starting with Hagemann's ester **156**, Johnson *et al*. first used an annulation sequence involving an alkylation with *β*-ethoxy-*γ*-bromocrotonate followed by hydrolysis and cyclisation of the resulting *β*-keto ester, then reduction using palladium on carbon[90] leading to the indanane **157**. A second annulation sequence, this time using ethyl vinyl ketone and phosphoric acid, next resulted in the tricyclic ester **158**. By reacting the unsaturated ketone **158** with methyl vinyl ketone in the presence of sodium ethoxide, the final A-ring was completed. The ring-D aromatic ester **159** was next resolved leading to the

enantiomerically pure material **159**. Reduction of the enone group in **159** finally gave the intermediate ketone **160** (Scheme 37).



Scheme 37 *Reagents and conditions* i) KO^{t}Bu, ethyl *β*–ethoxy-*γ*-bromocrotonate; ii) a) HCl, EtOH, b) piperidine, AcOH; iii) 10% Pd/C, *p*-cymene, reflux; iv) a) pyrrolidine, b) ethyl vinyl ketone, dioxane, c) AcOH, NaOAc; v) 85% H_3PO_4; vi) methyl vinyl ketone, NaOEt, EtOH; vii) ethylene glycol, HCl; viii) HCl, H_2O; ix) a) NaH, glyme, b) K, $NH_{3(l)}$; x) diazomethane; xi) DDQ, benzene; xii) resolution; xiii) a) NaOH, H_2O, b) HCl, H_2O, xiv) a) NaH, glyme, b) K, $NH_{3(l)}$; xv) diazomethane; xvi) DDQ, benzene.

The intermediate **160** was then converted into veratramine **60** in a further nineteen steps which synthesised the alkaloidal side-chain and completed the manipulation of the polycycle.

Our attention was drawn to this synthesis of veratramine **60** as we recognised that the tetracyclic, intermediate ketone **160** could be a potential target for a radical

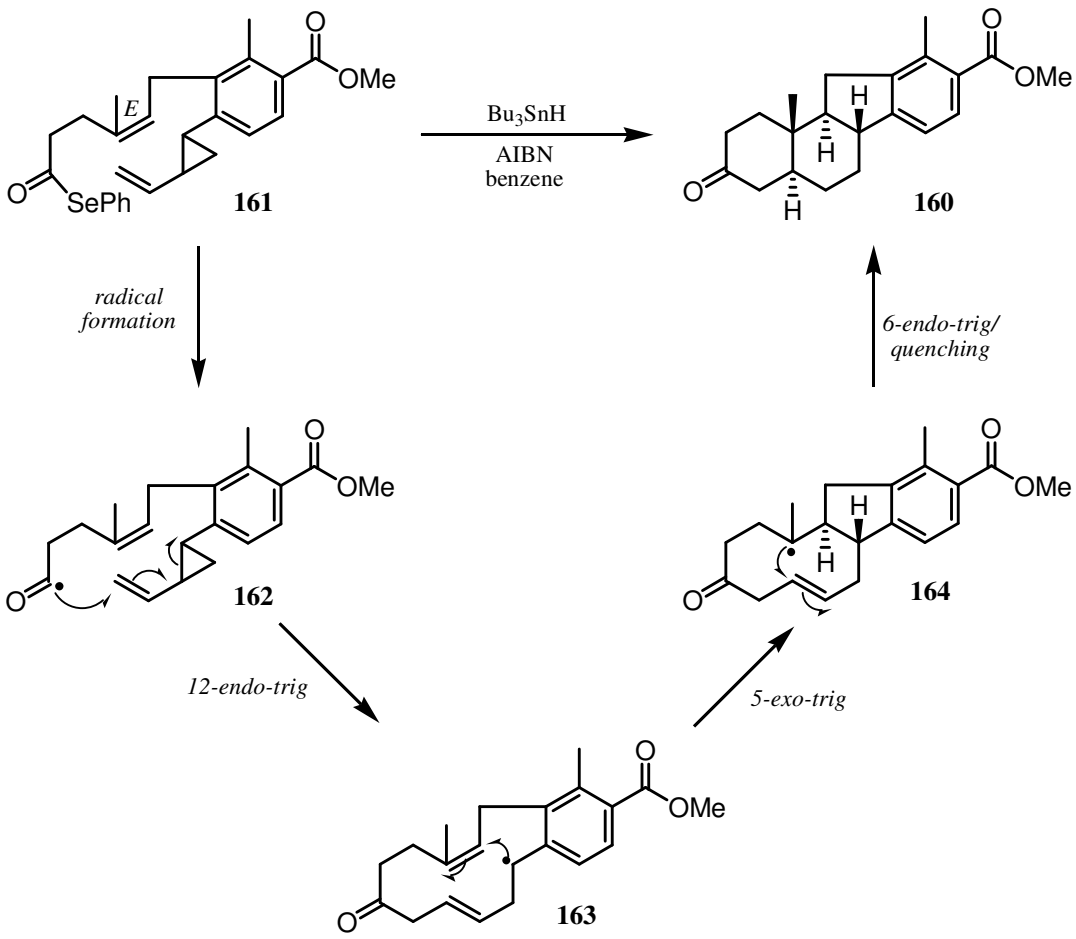
cascade strategy. The ring-D aromatic steroidal intermediate **160** did not have a great deal of functionality and a radical cascade approach to **160** would constitute a formal synthesis of veratramine **60**. After some deliberation the ketone **160** was chosen as a target for our research and we began the process of synthesising an appropriate precursor for its synthesis *via* a radical cascade.

A Ring-D Aromatic Model System

We decided to take a slightly different approach to our earlier study of cascade radical reactions (see page 36) in producing the ketone **160**. Instead of utilising an alkyl radical precursor adding into an enone electrophore, we decided to use a new macrocyclisation-transannulation radical cascade strategy which took advantage of the presence of the C-3 ketone in the target molecule **160**. We envisaged that this ketone could be derived from the acyl radical intermediate **162**, by adding into a vinylcyclopropyl electrophore *via* a 12-*endo*-trig radical macrocyclisation, leading first to the benzylic radical **163**. This new radical centre could then undergo transannulation *via* a 5-*exo*-trig cyclisation leading to the bicyclic **164** intermediate incorporating a tertiary radical centre. Finally, a 6-*exo*/*endo*-trig transannulation from **164** followed by a H-atom quench would give the desired 6,6,5,6 ring-D aromatic steroidal tetracycle **160** (Scheme 38).

The acyl radical centre **162** could be generated by various different means.[91] However, our research group has already made excellent use of seleno esters[92] in producing acyl radicals for the cascade syntheses and we were attracted to this particular strategy. After careful consideration and comparing the various different methods, we decided that the seleno ester would be the most suitable method for

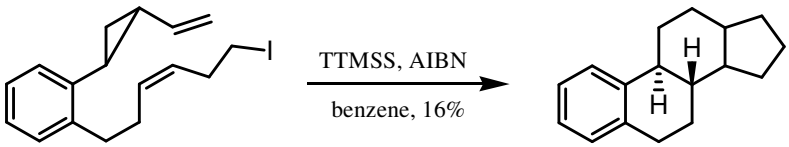
generating the acyl radical **162**. Hence, our radical cascade precursor target became the vinylcyclopropyl seleno ester **161**.



Scheme 38 A proposed radical cascade from the vinylcyclopropane **161** leading to the tetracycle **160**.

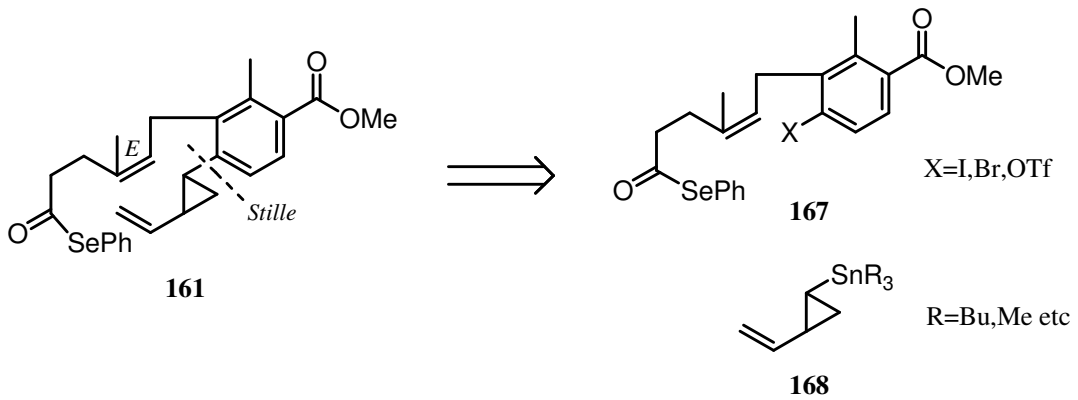
The proposed radical cascade approach to the tetracycle **160** from **161** had many attractions. Not least, if successful this would be the first reaction of its type whereby an acyl radical cascade into a vinylcyclopropyl electrophore had been demonstrated. We were also intrigued by the presence of the five-membered C-ring in **160** and how its presence would affect the cascade, having not found anything similar in the literature.

Using a vinylcyclopropyl, instead of an en- or ynone electrophore in synthesis is not without precedent. This strategy has already been used to good effect in our group's total synthesis of estrone **21** (see page 32),[72] and in elaborating the steroidal tetracycle **166** from the alkyl iodide **165**.[93]



165 **166**

We now considered an appropriate synthesis of the seleno ester intermediate **161**. The vinylcyclopropane portion in **161** could be synthesised *via* a linear sequence, *i.e*. constructing the cyclopropane and olefin separately step by step, but we were interested in a more convergent synthetic approach involving coupling the entire vinylcyclopropane unit to the aryl ring *via* palladium catalysis (Scheme 39).

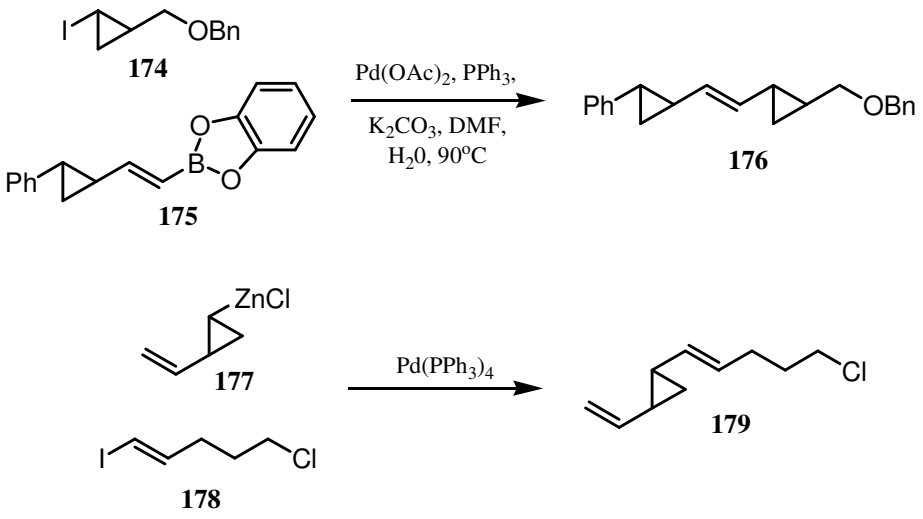


Scheme 39 A retrosynthetic analysis of the radical precursor **161**

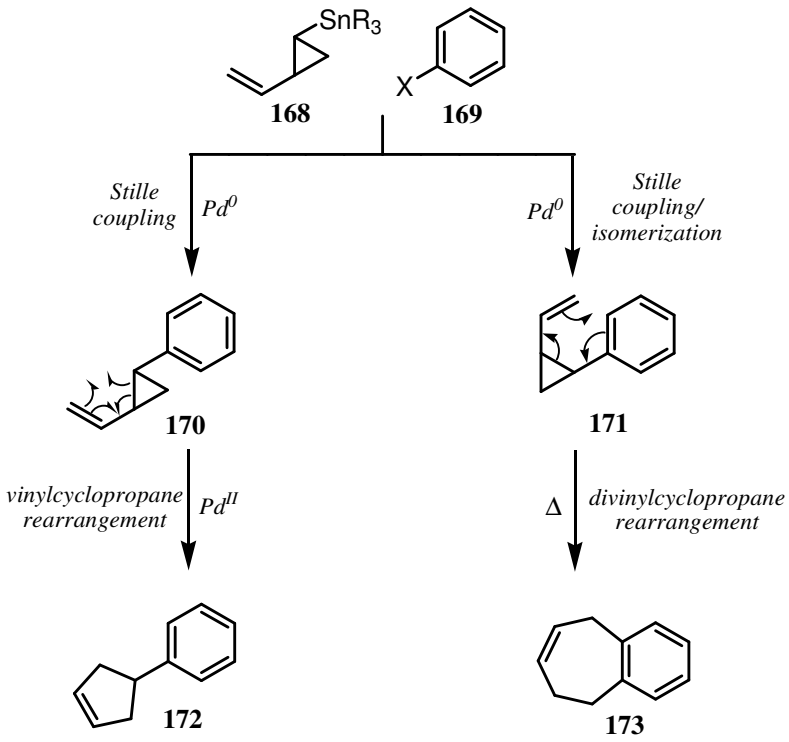
A Model Stille Coupling Reaction using Vinylcyclopropyl Stannanes

The Stille coupling reaction[94] between a vinylcyclopropyl stannane **168** and an aryl halide/triflate **170** is unprecedented, to our knowledge. Whilst this proposal has

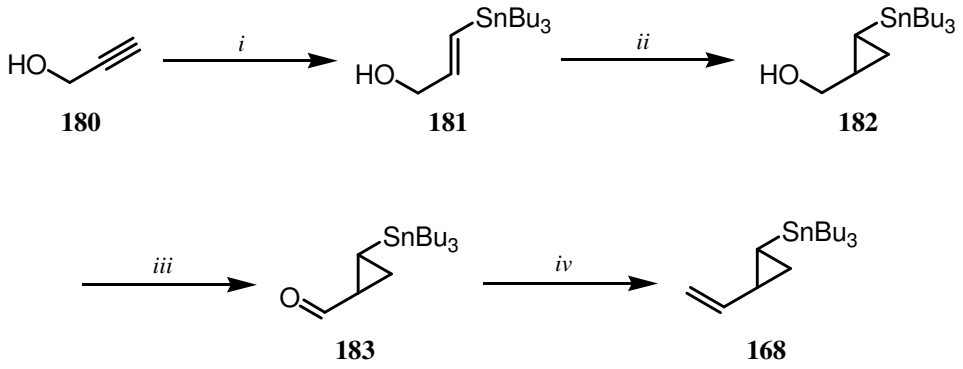
numerous advantages over a linear construction, it was also inherently risky for two main reasons: i) palladium(II) catalysed ring openings of vinylcyclopropanes are facile, and well known, **170→172** and ii) divinyl cyclopropane products can undergo thermal 'Cope' rearrangement in situ **171→173**.[95] A search of the literature revealed only two examples of organometallic coupling reactions involving vinylcyclopropanes. The first involved a Suzuki coupling of the boronate **175**[96] and the second a Negishi coupling reaction using the organozinc species **177** (Scheme 40).[97]



We decided first to model our proposed coupling reaction using the vinylcyclopropyl stannane **184**[97] and phenol triflate **169** under a range of conditions. Thus, propargyl alcohol **180** was first treated with tributyltin hydride and AIBN, which led to a mixture of *E* and *Z* isomers of the corresponding vinyl stannanes from which the desired *E*-vinyl stannane **181** was separated in 89% yield.



Scheme 40 Palladium catalysed coupling reactions involving vinylcyclopropanes, and potential side reactions.



Scheme 41 *Reagents and conditions* i) Bu_3SnH, AIBN, 100°C, 5h, 89%; ii) Et_2Zn, CH_2I_2, DCM, -50°C→-20°C, 48h, 74%; iii) IBX, DMSO, r.t, 20h, 96%; iv) $MePPh_3Br$, NaHMDS, THF, -78°C→r.t, 12h, 97%.

Subjecting the vinyl stannane **181** to a carefully temperature controlled Simmons-Smith reaction[98] next gave the cyclopropyl stannane **182**. The hydroxyl group in **182** was then oxidised using IBX[99] (which was found to be superior to Dess-Martin

or Swern oxidations), and the resulting aldehyde **183** was quickly converted into the target vinylcyclopropyl stannane **168**, using a Wittig reaction (Scheme 41).[100]

We were now in a position to attempt our model Stille coupling reaction between the vinylcyclopropyl stannane **168** and phenol triflate **169**. Unfortunately, and in spite of considerable effort, the initial attempts led to failure (Table 1).

Numerous different catalysts, solvents, additives and temperatures were utilised in our attempts to successfully couple the vinylcyclopropyl stannane **168** with phenol triflate **169**, including the use of the organocopper catalyst CuTC developed by Liebeskind *et al.*[101] This organocopper catalyst was seen as a possible way around the palladium catalysed side-reactions. However, both these and all the other attempts involving the vinylcyclopropyl stannane **168** were unsuccessful, either resulting in an unidentifiable mixture of non-products or returning starting materials unaffected by the reaction conditions.

Eventually we did uncover conditions which yielded some of the desired aryl vinylcyclopropane **184** from coupling between **168** and phenol triflate **169**. This was during an attempted coupling utilising a large excess of the Liebeskind copper catalyst (at 80^{o}C with lithium chloride) when the vinylcyclopropane **184** was detected in approximately 5% yield. However, our attempts to improve the yield of this copper catalysed coupling by varying additives, temperatures and reaction times, failed to improve upon this yield. Fortunately, more success was had when using the more traditional palladium acetate catalyst, under some less conventional conditions!

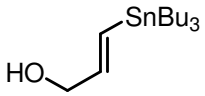
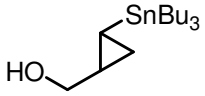
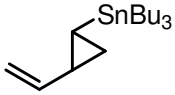
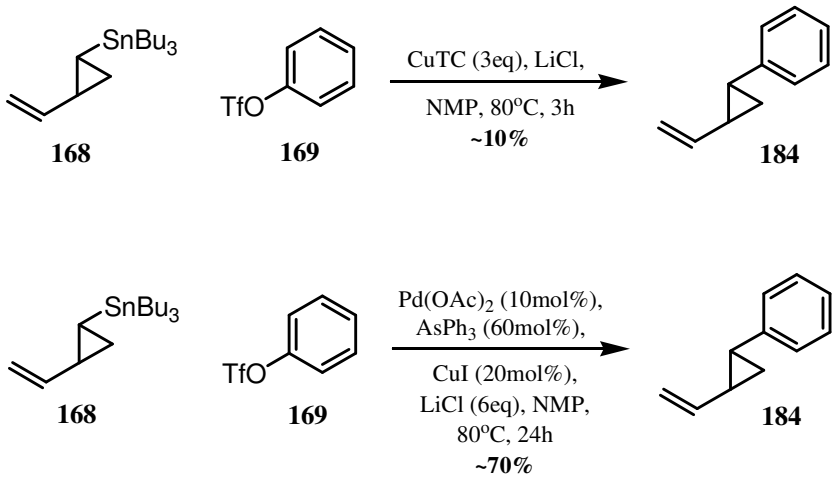
Stannane	Catalyst	Solvent	Additives	Temp./ Time	Result
	$Pd(PPh_3)_4$	Dioxane	LiCl	100°C/ 15h	94%
	$Pd(OAc)_2$	DMF	LiCl, CuI, $AsPh_3$	80°C/ 15h	67%
	$Pd(PPh_3)_4$	Dioxane	LiCl	100°C/ 15h	No Product
		NMP	CuI, CsF	r.t/ 24h	No Product
				80°C/ 12h	No Product
	$Pd_2(dba)_3$	NMP	CuI, $AsPh_3$	40°C/ 5h	No Product
			CuTC, $AsPh_3$		No Product
		DMF	$AsPh_3$		Rec. S.M
	$PdCl_2$	NMP	PCy_3, CuI, CsF	r.t/ 12h	Rec. S.M
				80°C/ 12h	No Product
	$Pd(OAc)_2$	DMF	LiCl(3eq), CuI $AsPh_3$	80°C/ 15h	No Product
			LiCl(6eq), CuI, $AsPh_3$		No Product
		NMP	CsF, $AsPh_3$, LiCl, CuI	r.t→80°C/ 24h	No Product
	CuTC	NMP	LiCl	r.t/ 24h	Rec. S.M
			CsF	40°C/ 15h	Rec. Phenol
			LiCl, CsF	r.t/ 12h	Rec. S.M
				80°C/ 12h	No Product

Table 1 Reagents and conditions for the reactions between **169** and the stannanes shown.

We surmised that possibly the presence of uncomplexed nucleophilic palladium was attacking the vinylcyclopropyl unit (both in the starting stannane **168** and any potential aryl vinylcyclopropane **184** product) and inhibiting the process. We therefore attempted to eliminate, or at least minimise, the level of nucleophilic

palladium. Whilst complexed palladium is required for the Stille reaction, we proposed that there will always be some quantity of free palladium in solution unless there is a large excess of ligand present. Several attempts at the coupling were therefore made, using three times the usual ligand to palladium ratio. Whilst this could slow down the rate of the coupling considerably, we hoped that it would also allow the product/starting vinylcyclopropanes to survive the coupling conditions. A significant pre-mixing period for the ligand and palladium catalyst was also introduced, to ensure that the palladium was all complexed before introducing the vinylcyclopropane **168**. Much to our satisfaction, using these modifications, an approximately 70% yield of the desired aryl vinylcyclopropane **184** was achieved (Scheme 42).

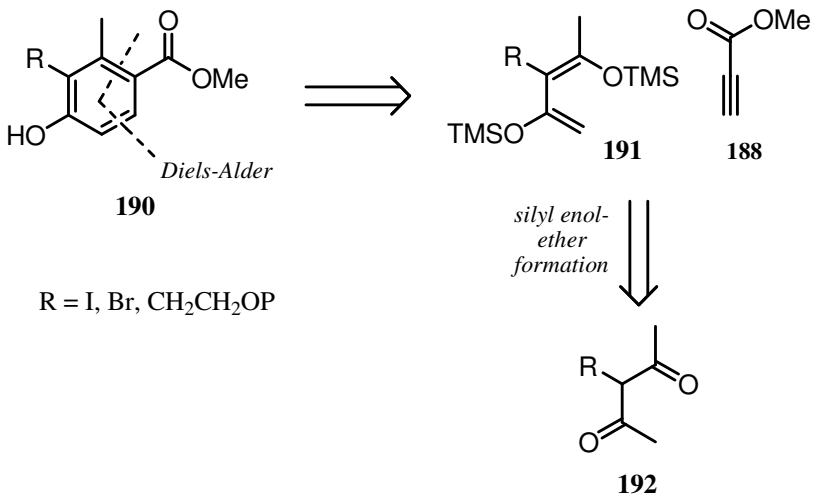


Scheme 42 Successful model coupling reactions between the vinylcyclopropyl stannane **168** and phenol triflate **169**.

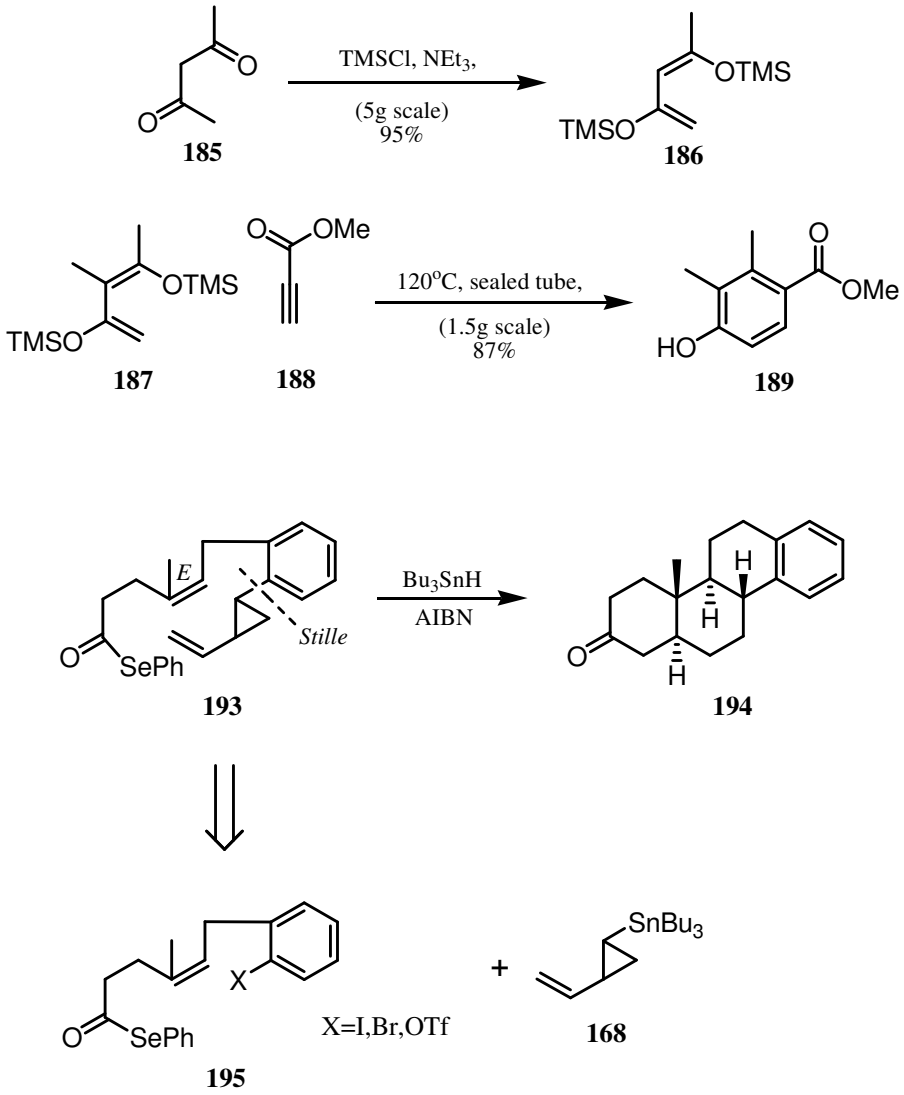
Having now successfully modelled what we believe to be the first Stille coupling reaction between a vinylcyclopropyl stannane and a phenol triflate, we turned our attention to a synthesis of the upper chain aryl unit **167** required for our projected synthesis of veratramine **60** (see page 61).

Retrosynthetic Analysis of the Precursor 161

The substituted aromatic ester **190** could be synthesised *via* conventional aromatic substitution chemistry from an appropriate precursor. However, a brief analysis revealed numerous selectivity issues together with a potentially long reaction sequence for this relativity simple building block. Therefore, we planned to utilise a Diels-Alder[102] approach to **190** using the 1,3-diene **191** and methyl propiolate **188**. Whilst this may seem to be a sterically demanding Diels-Alder reaction, there is precedent from earlier studies of Pulido *et al.*[103] The 1,3-diene **191** could be derived from the 1,3-diketone **192** using a procedure similar to that devised by Rutledge *et al* (Scheme 43).[104] Although initial forays into the synthesis of the 1,3-diene **191** were successful, we decided that it would be prudent to simplify the system further for the purpose of modelling the planned radical cascade we therefore planned to first synthesise the seleno ester **193** with no substituents in the aryl ring (Scheme 44).



Scheme 43 The proposed synthesis of the aryl building block **190**.



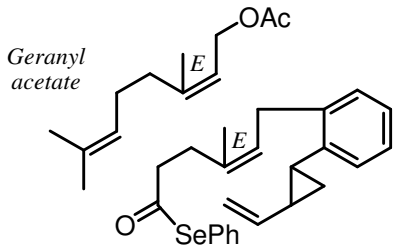
Scheme 44 The model radical precursor **193**.

Synthetic Routes to the Radical Precursor 193

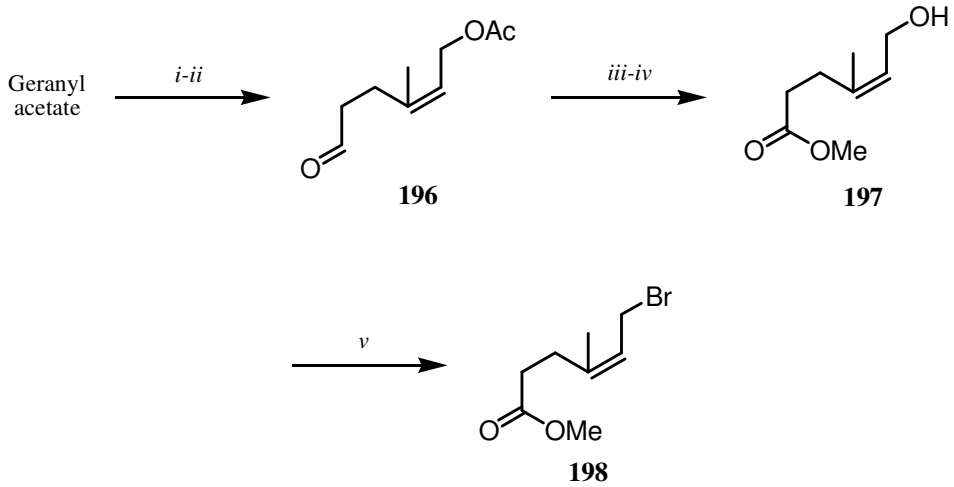
Analysis of the C-6 alkenyl chain in the target radical seleno ester **193** presented us with the possibility of using a derivative of geraniol as a basis for its synthesis, and this prompted us to disconnect the alkenyl chain to the C-6 allylic bromide **198**.

The synthesis of **198** was based upon a combined and modified version of similar syntheses described by Plé *et al.*[105] and by Canonica *et al.*[106] Thus, geranyl acetate was first oxidised selectively using 3-chloroperbenzoic acid and the resulting

vicinol diol was then cleaved with periodic acid, leading to the aldehyde **196**. Oxidation of **196** to the corresponding carboxylic acid using Jones reagent followed by esterification and cleavage of the acetate protecting group using acidic methanol next gave the hydroxyl ester **197**. Several methods were examined for the conversion of the alcohol **197** into the bromide **198**, and phosphorus tribromide in hexane at -40^{o}C was found to be the most effective (Scheme 45).



193

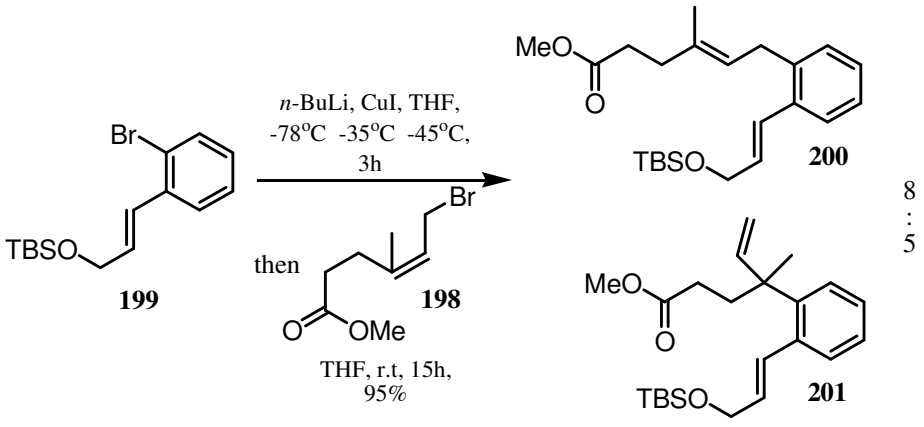


196 **197** **198**

Scheme 45 *Reagents and conditions* i) *m*-CPBA, DCM, 0^{o}C, 12h; ii) H_5IO_6, THF/H_2O, 0^{o}C, 2h, 66% (over 2 steps); iii) Jones reagent, acetone, 0^{o}C, 93%; iv) MeOH, H_2SO_4, r.t, 12h, 79%; v) PBr_3, hexane, -40^{o}C, 1.5h, 94%.

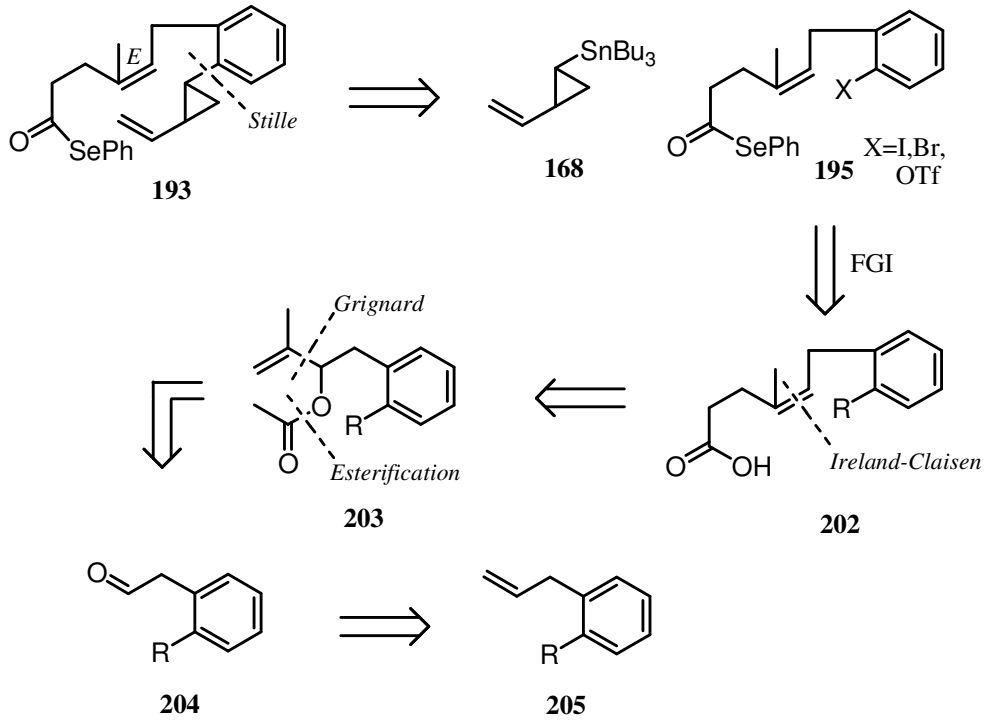
Our next synthetic step was to couple the bromide **198** to an appropriate aryl unit. Several different methods for this coupling reaction were attempted. Unfortunately, after extensive investigations, the best method using an organocopper intermediate,

whilst resulting in the desired product, also led to an undesired and inseparable by-product. For example, a coupling reaction between the aryl bromide **199** and the allyl bromide **198** resulted in a 95% yield of an 8:5 mixture of the trisubstituted olefin **200** and the undesired isomer **201**, resulting from S_N2' attack on **198**. Unfortunately we were not able to separate these isomers and attempts to reduce the amount of the unwanted olefin **201** were unsuccessful; this route was therefore abandoned.



A change of tactic prompted us to attempt a similar synthesis of the C-6 alkenyl chain in **193** by performing a coupling reaction first followed by manipulating the geranyl chain whilst it was attached to the aryl unit. Thus, by utilising a similar organometallic coupling reaction we united an aryl iodide to geranyl bromide in excellent yield, and with no evidence for the co-formation of unwanted isomers. Unfortunately, however, whilst the epoxidation of the product proceeded smoothly, yields for the subsequent cleavage step etc were very low yielding and were accompanied by significant side-products.

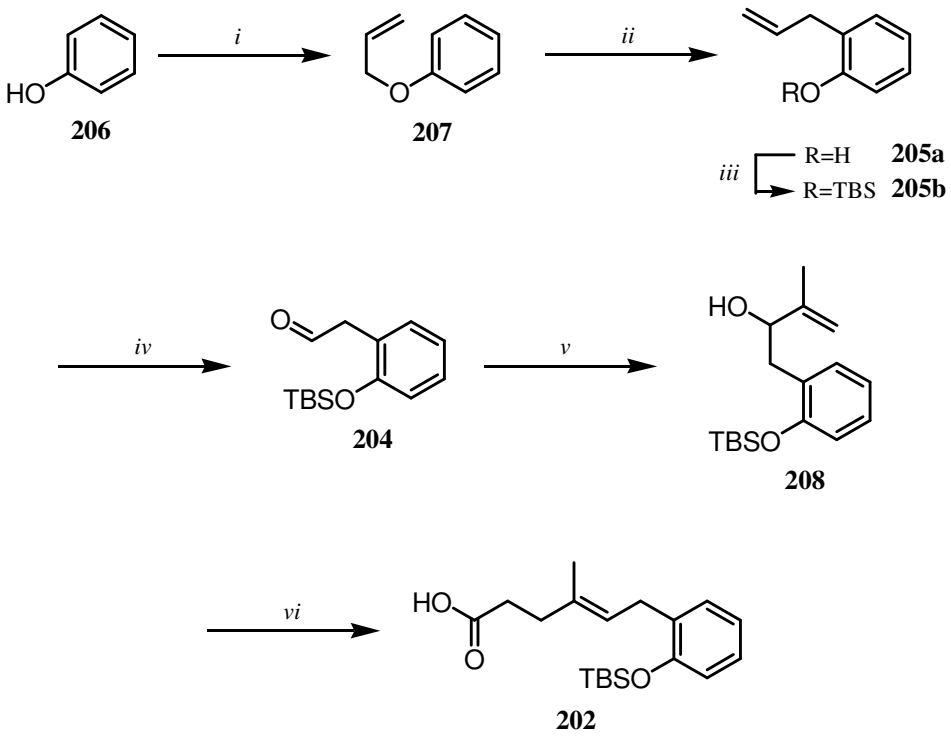
After this disappointing start to our synthetic approach to **193**, we decided to alter our strategy to the C-6 alkenyl chain in **195**. Thus, the seleno ester **195** could be constructed from the carboxylic acid **202**[91] which itself could be derived from the acetate **203** *via* an Ireland-Claisen rearrangement.[107] In turn, the acetate **203** should be easily accessible from the aldehyde **204** using a conventional Grignard reaction[74] using isopropenylmagnesium bromide, followed by treatment with acetic anhydride. The aldehyde **204** could be synthesised from the known alkene **205** (Scheme 46).



Scheme 46 A new retrosynthetic analysis of the radical precursor **193**.

Thus, following some literature precedent,[108] phenol **206** was first converted into the corresponding allyl ether **207**, which then underwent Claisen rearrangement at 190^{o}C leading to the corresponding allylphenol **205a**. Protection of **205a** as the *tert*-butyldimethylsilyl ether **205b** followed by oxidative cleavage using potassium

permanganate and periodic acid next gave the aldehyde **204** in excellent yield on a large scale. The Grignard reaction between **204** and isopropenylmagnesium bromide performed poorly, giving the isopropenyl alcohol **208** in a disappointing 35% yield. This, together with the low yield achieved in the subsequent Ireland-Claisen reaction, led us to eventually abandon this route to **195** (Scheme 47).



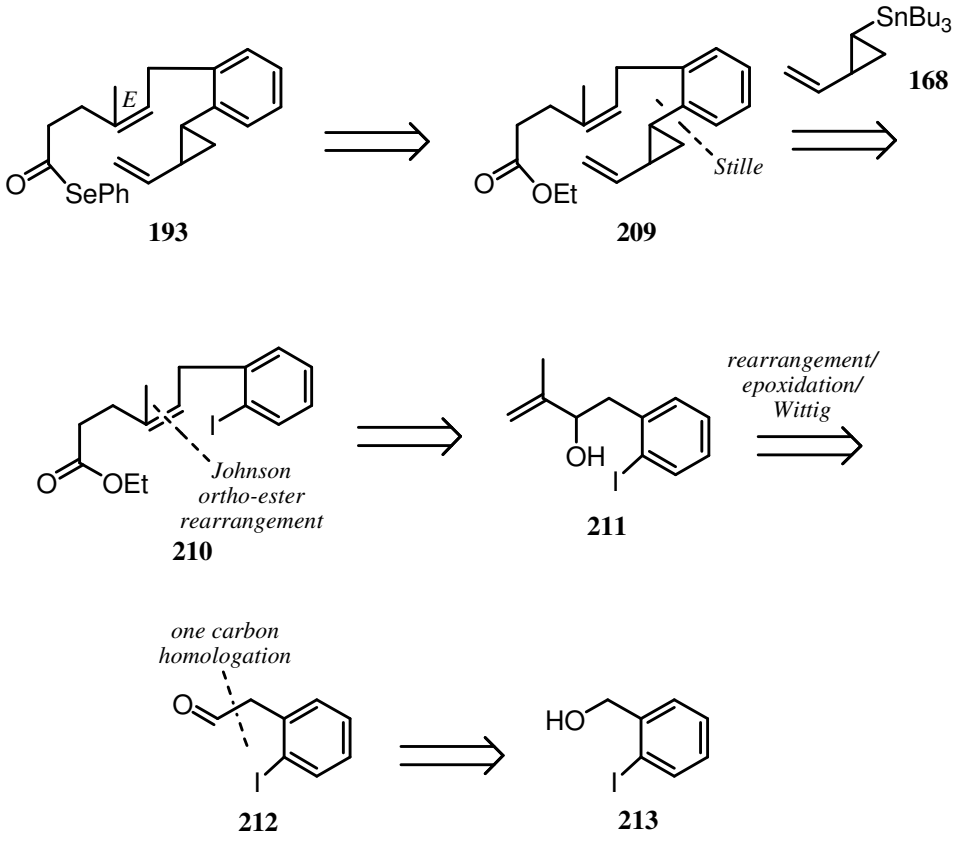
Scheme 47 *Reagents and conditions* i) Allyl bromide, K_2CO_3, DMF, r.t, 12h, 98%; ii) 190°C, neat, 5 days, 96%; iii) TBSCl, Imid, DMF, r.t, 3h, 69%; iv) a) $KMnO_4$, H_2O/IPA, r.t, ~10mins, b) H_5IO_6, H_2O, r.t, ~15mins, 88%; v) Isopropenylmagnesium bromide, $BF_3.OEt_2$, THF, -78°C, 2h, 45%; vi) a) Ac_2O, py, DMAP, r.t, 12h, b) LDA, TMSCl, THF/HMPA, -78°C→r.t, 12h, 12%.

Synthesis of the Radical Cascade Precursor 193

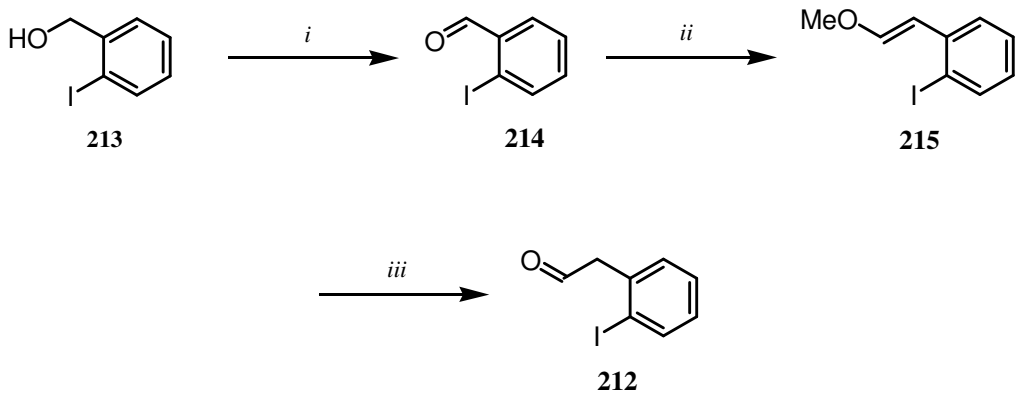
In light of the low yields achieved for the isopropenyl Grignard reaction with the aldehyde **204** and the subsequent Ireland-Claisen rearrangement, a new synthetic plan was devised based on a Johnson ortho-ester rearrangement.[109] Our synthesis of

the aldehyde **204** was also modified in order to allow for a change in the leaving group for the subsequent Stille reaction and to improve overall yields.

Thus, our new retrosynthetic analysis began from the aryl iodide **210** which we planned to produce from the allylic alcohol **211** *via* an *E*-selective Johnson ortho-ester rearrangement. The allylic alcohol **211** in turn, would be produced from the aldehyde **212** derived in three known[110] straightforward steps from 2-iodobenzyl alcohol **213** (Scheme 48).



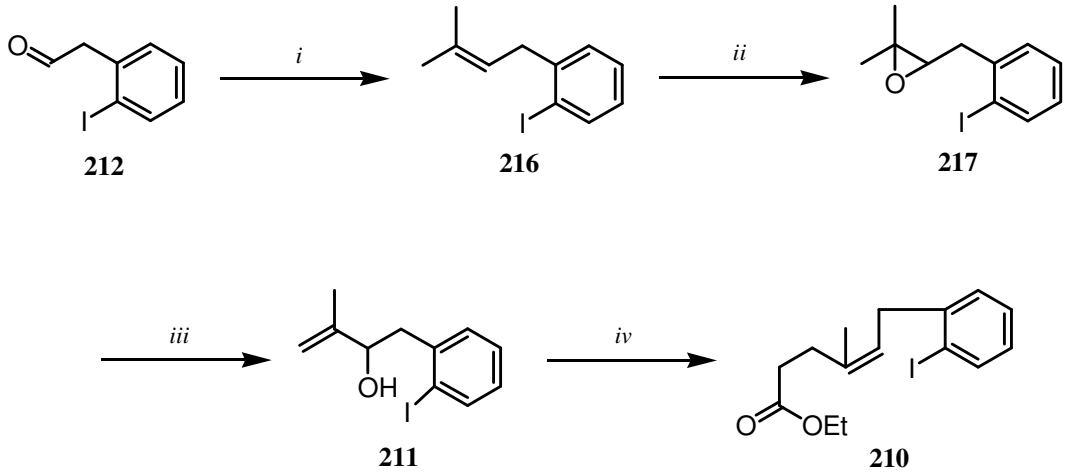
Scheme 48 A revised retrosynthetic analysis of the radical cascade precursor **193**.



213 **214** **215** **212**

Scheme 49 *Reagents and conditions* i) MnO_2, DCM, r.t, 24h, 94%; ii) Ph_3PBrCH_2OMe, KO^{t}Bu, THF, r.t, 12h, 92%; iii) Formic acid, DCM, r.t, 4.5 days, 88%.

A Wittig reaction between the aldehyde **212** and isopropyltriphenylphosphonium iodide next gave the trisubstituted alkene **216** in good yield. Epoxidation of **216** followed by Lewis acid catalysed rearrangement[111] of the resulting epoxide in the presence of aluminium isopropoxide led to the allylic alcohol **211** in equally good yield, on large scale.

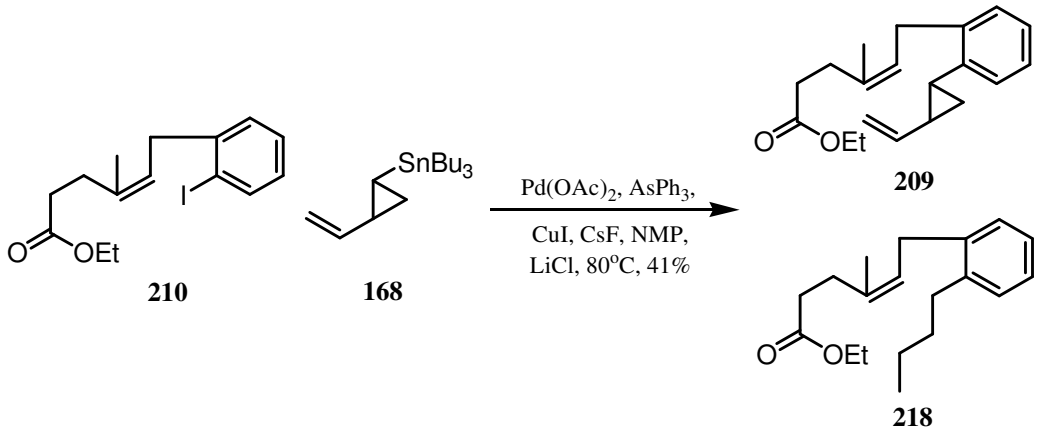


212 **216** **217** **211** **210**

Scheme 50 *Reagents and conditions* i) Isopropyltriphenylphosphonium iodide, BuLi, THF, 0^{o}C, 3h, 82%; ii) *m*-CPBA, DCM, 0^{o}C→r.t, 24h, 84%; iii) Al(O^{i}Pr)$_3$, tol, reflux, 12h, 83%; iv) Propionic acid, triethyl orthoacetate, 100^{o}C, Dean-Stark, 4 days, 91%.

The key rearrangement of the ortho ester derived from the allylic alcohol **211**, in the presence of freshly distilled propionic acid and triethylorthoacetate at 100°C, then gave the desired *E*-trisubstituted olefin ethyl ester **210** in 91% overall yield (Scheme 50).

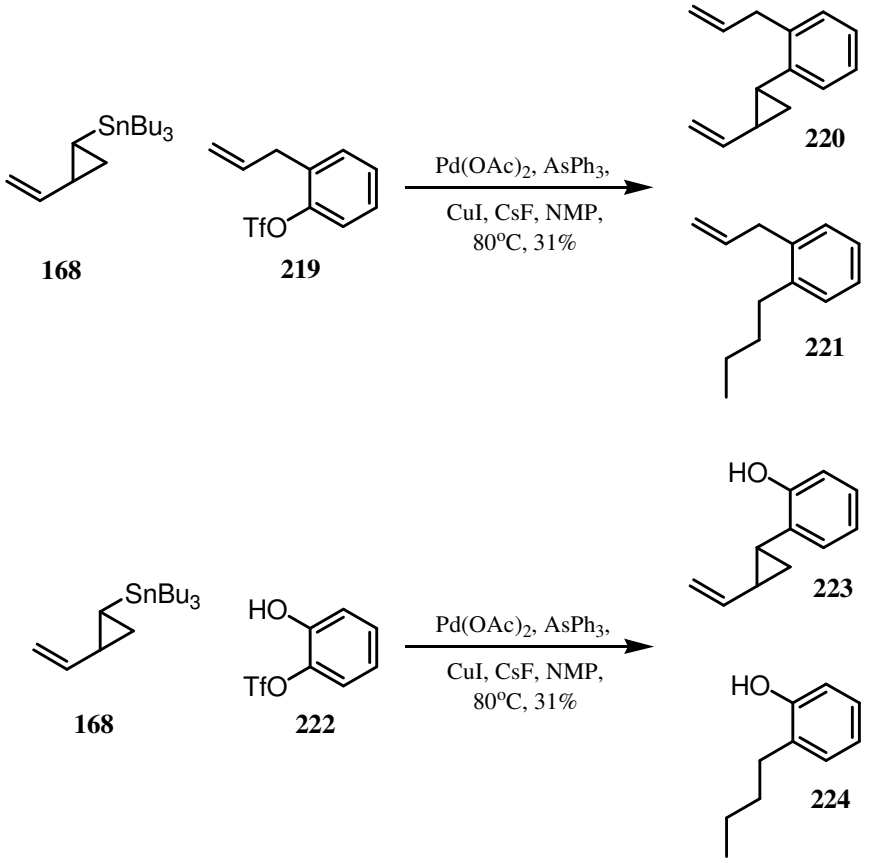
We were now in a position to examine the key Stille coupling reaction between the aryl iodide **210** and the vinylcyclopropyl stannane **168**. Using the previously developed reaction conditions (notably the large excess of arsine ligand and an extended premixing period) we coupled **210** with **168** and gratifyingly isolated the desired coupling product **209**. However, the required product **209** was accompanied by the arylbutane **218** as a by-product which we were unable to separate from the vinylcyclopropane **209**.



210 **168** **209** **218**

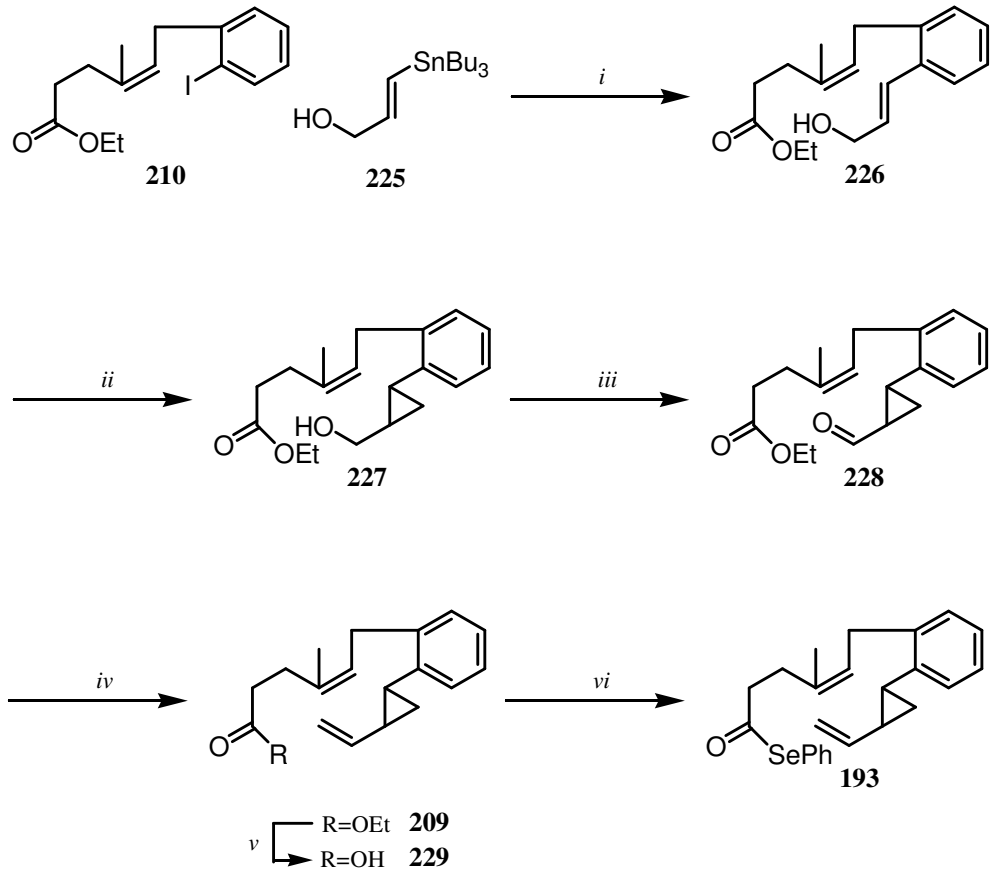
We postulated that this aryl butane by-product **218** arose from the Stille cross-coupling of one of the three butyl groups attached to the tin centre in the stannane **168** instead of the vinylcyclopropane group. Since this outcome was not observed in the model system it was an interesting and surprising result. Indeed, whilst the Stille coupling between an aryl unit and a butyl stannane unit is precedented, this

has only been reported using a tetrabutyl tin reagent. The situation whereby the sp^3 butyl group in the vinylcyclopropyl stannane **168** migrates in competition with the anticipated (sp^2/sp^3) cyclopropane group is surprising and we suggest that steric factors are the most likely cause of this unusual outcome. Indeed, when we went back to the model system (see page 66) and modified the substrate to include an ortho substituent to the triflate unit, a similar by-product *i.e.* **218**, resulting from butyl migration was detected (see below).



To our frustration we were unable to separate the aryl butane **218** from the aryl vinylcyclopropane **209** and continue with the synthesis of the radical cascade precursor **193** from the intermediate.

We ultimately decided to synthesise the seleno ester **193** from the aryl iodide **210** first performing a Stille coupling reaction with (*E*)-3-(tributylstannyl)prop-2-en-1-ol **225** leading to **226**. This seemingly straightforward reaction unexpectedly resulted in a mixture of *E*/*Z* alkene isomers with the *Z*-alkene dominating. Fortunately we were able to isomerise the *Z*-isomer to the more stable *E*-isomer by adding a catalytic amount of iodine adsorbed on silica to a solution of the two isomers in benzene and leaving the solution in daylight for twelve hours.



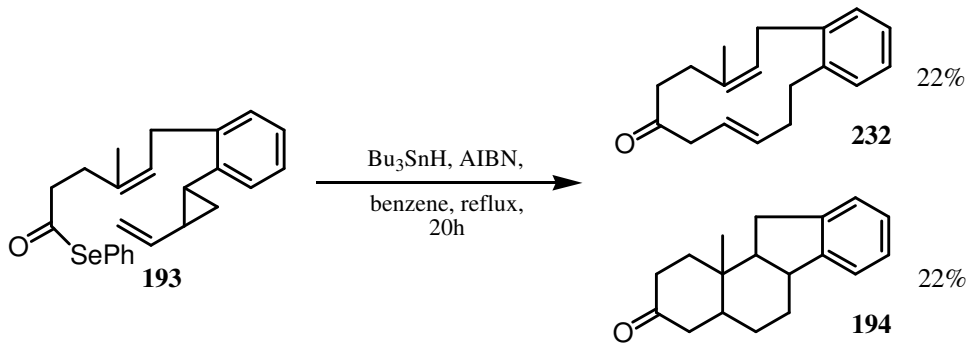
Scheme 51 *Reagents and conditions* i) a) $PdCl_2(PPh_3)_2$, LiI, LiCl, DMF, 80°C, 16h, b) Iodine on silica, *hν*, benzene, r.t, 12h, 60%; ii) Et_2Zn, CH_2I_2, DCM, r.t, 48h, 82%; iii) IBX, DMSO, r.t, 12h, 70%; iv) $MePPh_3Br$, NaHMDS, THF, -78°C→r.t, 12h, 93%; v) LiOH, H_2O/MeCN, r.t, 24h, 96%; vi) NPSP, Bu_3P, benzene, r.t, 24h, 55%.

A Simmons-Smith cyclopropanation reaction with the *E*-alkene **226** next gave the cyclopropane **227**. Oxidation of **227** using IBX, followed by a Wittig reaction between the resulting aldehyde **228** and methyltriphenylphosphonium bromide then gave the vinylcyclopropane **209**. Saponification of the ester group in **209**, using lithium hydroxide then gave the carboxylic acid **229**. However, we encountered several problems when attempting to convert the acid into the corresponding seleno ester **193** using *N*-(phenylseleno) phthalimide and tributylphosphine in dichloromethane. Attempts to form the seleno ester **193** under the same conditions we had used with an earlier model compound resulted in decomposition of the vinylcyclopropane unit in **193**. Postulating that this was most likely due to nucleophilic attack by benzeneselenyl anion into the vinylcyclopropane unit in **193** we changed the solvent from dichloromethane to the less polar benzene and this simple modification gave the seleno ester **193** in good yield (Scheme 51).

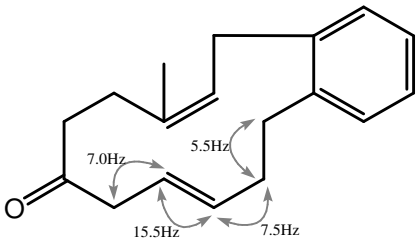
With a reasonable quantity of the seleno ester **193** in hand, we now turned our attention to investigating the long-awaited radical cascade sequence shown in Scheme 38.

The Macrocyclisation-Transannulation Radical Cascade from the Seleno Ester 193

Treatment of the seleno ester **193** with tributyltin hydride and AIBN in refluxing benzene resulted in the formation of two major (~22% each) and three minor products (1-8% yield), all of which could be separated by column chromatography.

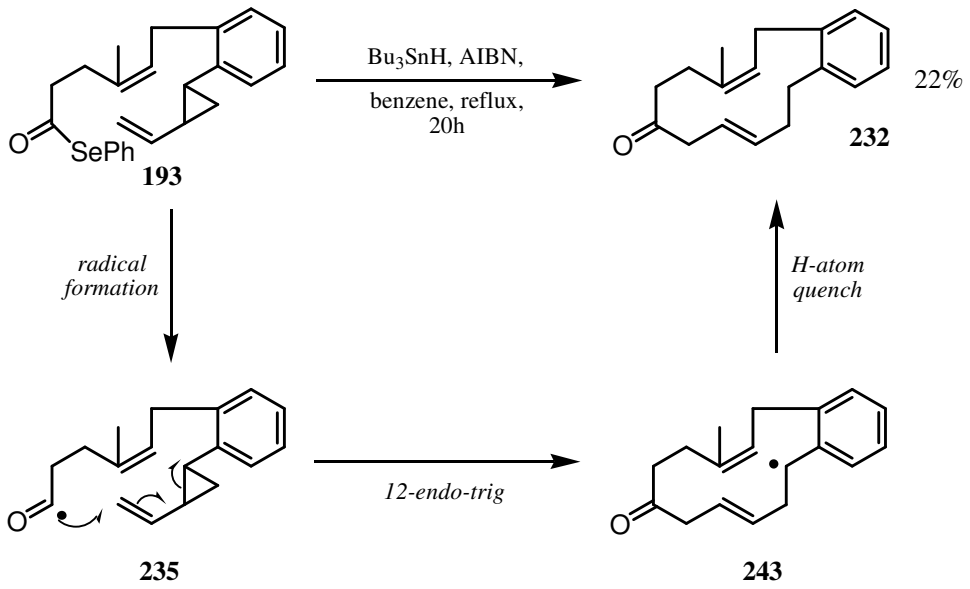


The structure of the first major product (~22% yield) was shown to be the macrocyclic dienone **232**. The structure followed from examination of its proton and carbon NMR spectroscopic data, alongside a 2D NMR analysis; a COSY analysis led to the proton coupling data around the macrocycle shown below,



232

and allowed the assignment of *E*-stereochemistry to both of the alkene bonds in the macrocyclic dienone. The isolation of **232** provided evidence for the addition of the first-formed acyl radical **235**, produced from the seleno ester **193**, into the vinylcyclopropane electrophore with concomitant cyclopropane ring cleavage, leading to the benzylic radical intermediate **243** (Scheme 52). Presumably a proportion of this stabilised radical centre is then quenched by a H-atom source leading to the observed product. Any benzylic radical centres which are not quenched at this stage, undergo two consecutive transannular cyclisations producing the second major product of the reaction *i.e*. the tetracyclic ketone **194**.



Scheme 52 Formation of the macrocycle **232** from the seleno ester **193**.

The second major product isolated from the reaction mixture showed proton, carbon and mass spectral data consistent with a tetracyclic compound, derived from a "completed" radical-mediated macrocyclisation-transannulation cascade. The spectra, together with analytical HPLC data, demonstrated that the compound was present as a 1:1 mixture of diastereoisomers. Reverse phase HPLC (acetonitrile/water gradient elution) allowed separation of the diastereoisomers, one of which was obtained pure, whilst the second was contaminated with *ca* 15% of the other diastereoisomer.

Analysis of the carbon-13 NMR spectrum of the pure diastereoisomer showed eighteen resonances (6 aromatic, 11 aliphatic and a C=O resonance). A DEPT analysis confirmed four aromatic and three aliphatic methine, six aliphatic methylene and a single methyl signal, leaving one aliphatic quaternary and two aromatic quaternary carbons.

The proton NMR spectrum of this diastereoisomer showed seven distinct regions of overlapping proton signals between δ1.3 and δ1.9ppm, and one double doublet

(J = 7.0 and 2.0Hz) and a multiplet in the aromatic region. From an HMQC experiment all of the proton signals could be correlated with their carbon centres. To establish the carbon connectivity both COSY and HMBC experiments were then performed. Starting from the readily assigned benzylic proton signals, strong correlations were observed around the tetracycle.

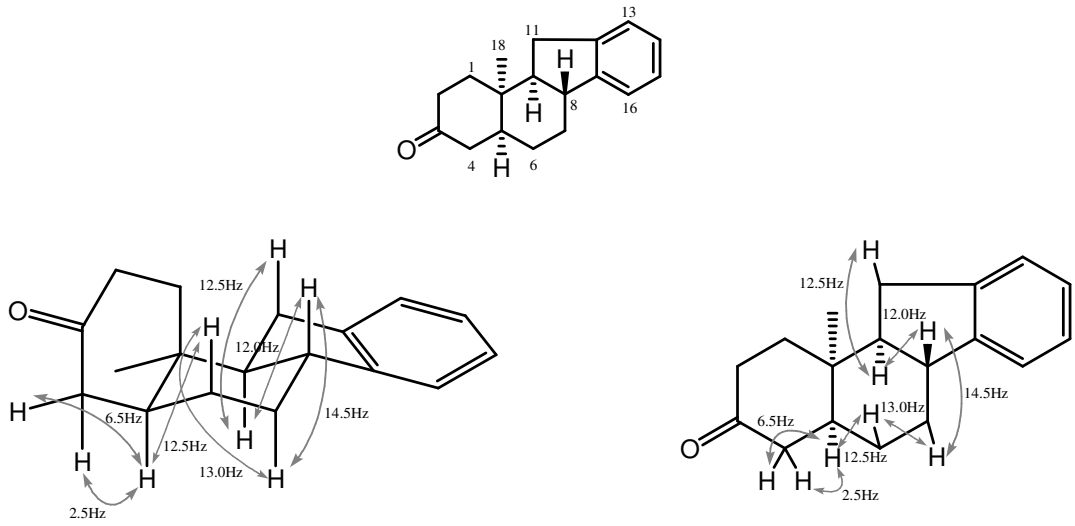


Figure 4 Pertinent J values for the diastereoisomer **194b**.

As Figure 4 illustrates, the vicinal coupling of the B/C ring junction in this diastereoisomer was 12.0Hz which was compatible with a *trans*-ring fusion. The dihedral angles for the B-ring protons demonstrate that this ring adopts a chair conformation. However, the C-4/C-5 relationship shows no diaxial coupling (6.5 and 2.5Hz) demonstrating that the A/B ring junction cannot be *trans*. This evidence together with the high carbon-13 shift of the methyl carbon (δ24.8ppm) also led us to propose a *syn* relationship between the C-18 methyl and the H-9 proton. Comparison of the observed J-values with those calculated from all possible configurations/conformations also supported these observations. Indeed, such

NMR coupling patterns established the *cis*, *syn*, *trans* stereochemical pattern, shown in Figure 4 for this diastereoisomer.

Carbon-13 and DEPT NMR experiments on the other diastereoisomer established the same carbon environments as determined for **194b**, and COSY, HMQC and HMBC experiments confirmed a similar skeletal pattern. However, whilst the B/C ring junction showed a similar *trans* coupling (12.5Hz), and the diaxial couplings of the B-ring strongly suggested that it too was held in the chair conformation, the remaining *J*-values differed from those found in **194b**.

Significantly the C-4/C-5 relationship demonstrated a *trans* diaxial coupling (13.5Hz). This strongly inferred a *trans* relationship for the A/B ring junction. A comparison of the observed *J*-values for **194a** with those calculated from all possible configurations/conformations also supported this observation, and the methyl carbon-13 resonance at δ11.6ppm together with these comparisons supported a *trans*, *anti*, *trans* stereochemical pattern (Figure 5).

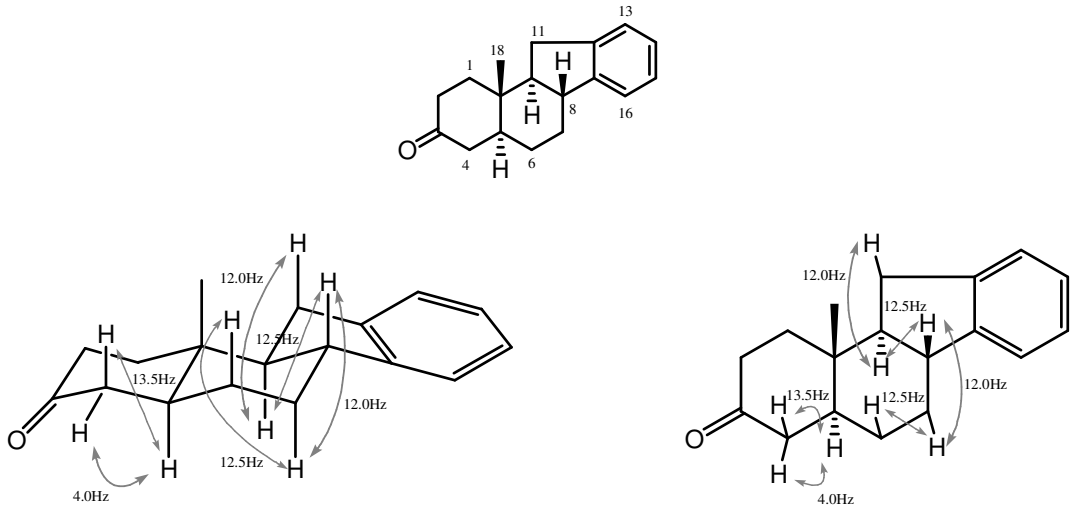
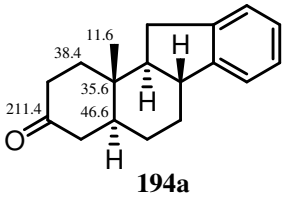
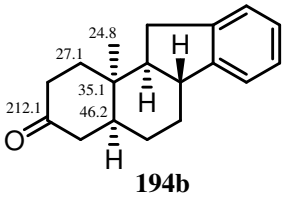


Figure 5 Pertinent *J* values for diastereoisomer **194a**.

Bhattacharyya *et al.*[112] have reported the tetracycle **194** previously, but unfortunately only a melting point was recorded, with no NMR spectroscopic details or stereochemical information. However, all our spectroscopic data support the assignment of **194** as the desired 6,6,5,6 ring-D aromatic steroid. Unfortunately, we were not able to grow a suitable crystal for X-ray crystallographic analysis.



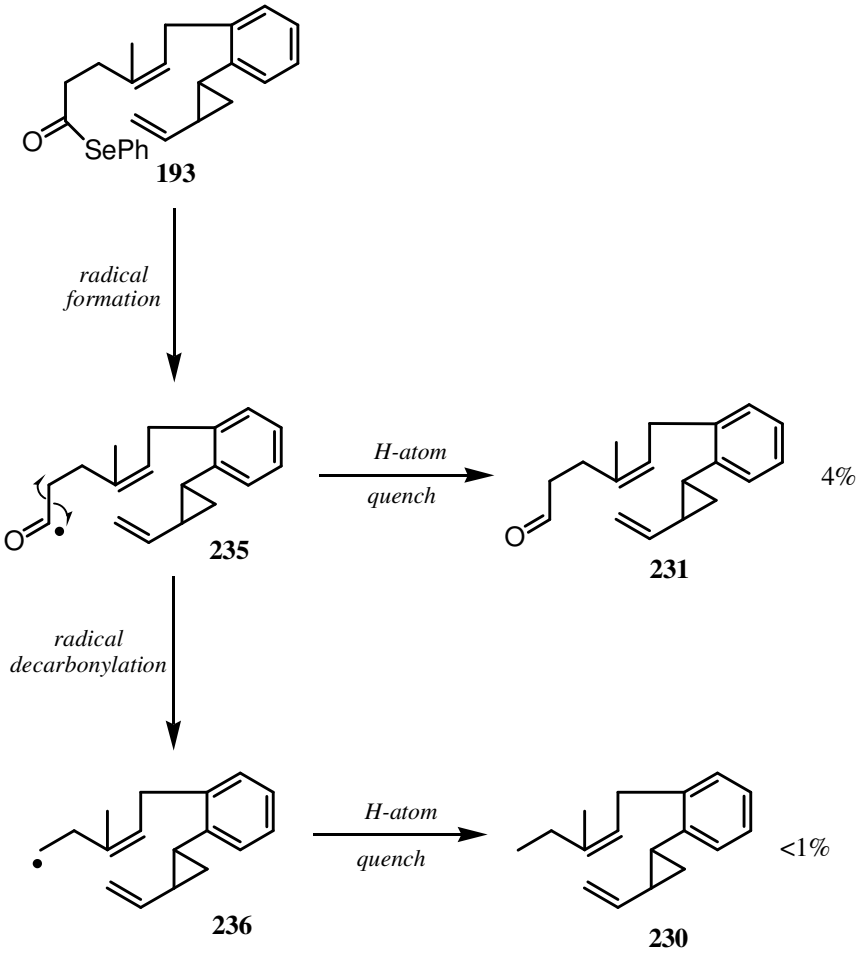
194a



194b

NMR spectroscopic analysis of the least polar of the minor products (<1%) revealed that it had retained the vinylcyclopropane unit in the starting material, but that the selenyl ester group was missing. Further analysis of all the spectroscopic data, identified this product as that resulting from radical decarbonylation of the first formed acyl radical intermediate, *i.e.* **230**

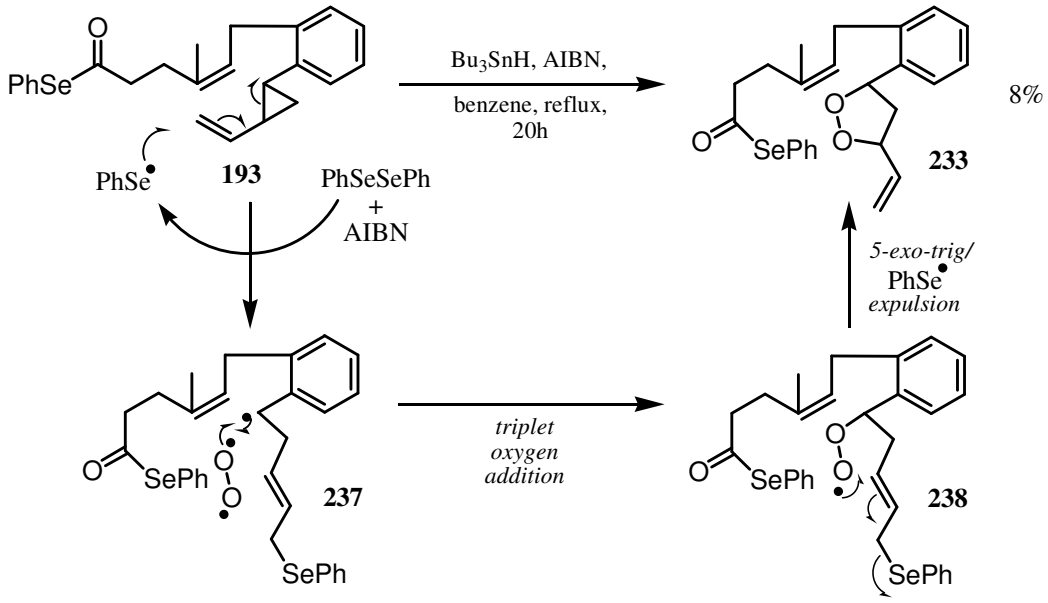
The second minor product (4% yield) was also found to have retained the vinylcyclopropane unit in the starting material, but its NMR spectroscopic data also showed the presence of a saturated aldehyde group. Further analysis established that the aldehyde resulted from H-atom quenching of the acyl radical precursor, *i.e.* **231** (Scheme 53).



Scheme 53 Formation of the products **230** and **231** from **193**.

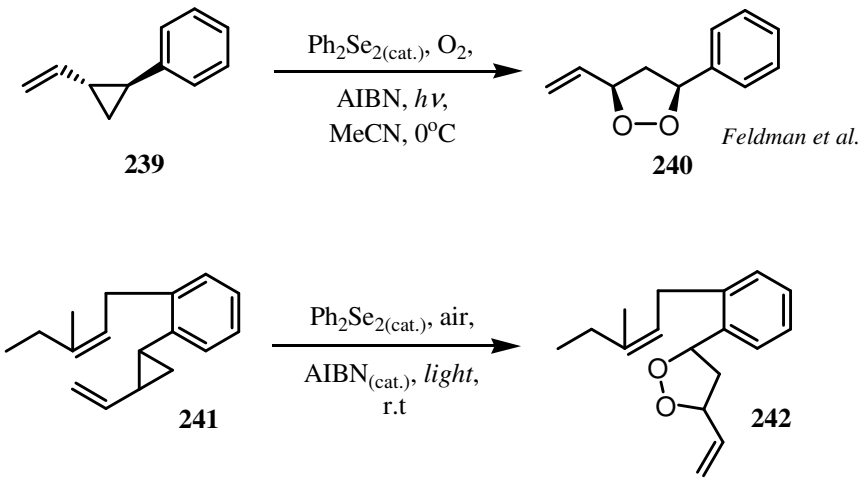
The most polar minor product, isolated in 8% yield, had an M + O_2 molecular ion in its mass spectrum, and NMR spectroscopic analysis showed that it had retained all the proton signals associated with the C-6 alkenyl chain, including those of the seleno ester group. However, the resonances in the proton NMR spectrum associated with the cyclopropane ring in the starting material were shifted downfield in this product. We ultimately assigned the structure of the compound as the dioxolane **233** resulting from phenylselenyl radical-catalysed addition of oxygen across the cyclopropane ring in the starting material (Scheme 54). This outcome was unexpected, especially in view of the fact that the radical reaction was conducted under argon, with oxygen strenuously eliminated from the system before

and during the reaction. We presume that **233** was produced when the reaction had been cooled, and the flask opened to the atmosphere. Any remaining starting material **193** and diphenyl diselenide (a product which was also isolated from the reaction) could then mix with residual AIBN and catalyse the addition of oxygen across the cyclopropane ring in **193**. Indeed, this type of reaction is not unknown, and Feldman *et al.*[113] have produced the dioxolane **240** from the aryl vinylcyclopropane under comparable conditions.



Scheme 54 Formation of the dioxolane **233** from the vinylcyclopropane **193**.

To provide further evidence for this hypothesis, we treated a sample of the vinylcyclopropane **241** with very small quantities of diphenyl diselenide and AIBN, and found that it was entirely converted into the corresponding dioxolane **242** within five minutes.



In conclusion, we have succeeded in developing a new approach to the 6,6,5,6 ring-D aromatic steroid **194** from the vinylcyclopropyl seleno ester **193**, *via* a novel free radical macrocyclisation-transannulation cascade reaction. Treatment of the seleno ester **193** with tributyltin hydride and AIBN was shown to lead a 1:1 mixture of diastereoisomers of **194**, identified as the *trans*, *anti*, *trans* isomer **194a** and its methyl epimer **194b**. Also isolated from the cascade as a major product, was the macrocycle **232**. Small amounts of the products of direct reduction of **193**, *i.e*. **231**, the decarbonylated material **230**, and the dioxolane **233** were also isolated. These studies, once again, have demonstrated that with careful planning radical cascade reactions can lead to complex products, with the desired stereochemistry, from simple precursors, in a single step.

Experimental

General Details

Proton magnetic resonance chemical shifts (δ_H) were recorded in parts per million (ppm), are referenced to the residual solvent peak ($CHCl_3$ = 7.26ppm), and are recorded to two decimal places. Coupling constants (*J*), are reported to the nearest 0.5Hz. The multiplicity of each signal is designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent) and br (broad). Proton magnetic resonance spectra were recorded on a Brüker DRX360 (360.1MHz), Brüker AV400 (400.1MHz) or Brüker DRX500 (500.1MHz) spectrometer, at ambient temperature, unless otherwise stated. All assignments are confirmed by ^1H–^1H COSY, ^1H–^{13}C HMQC and/or NOE correlations, where necessary.

Carbon magnetic resonance chemical shifts (δ_C), were recorded in parts per million (ppm), referenced to the residual solvent peak ($CDCl_3$ = 77.1ppm) and are recorded to one decimal place. The multiplicity of each signal was determined by DEPT analysis and was designated by the following abbreviations: s (singlet, quaternary), d (doublet, CH), t (triplet, CH_2), q (quartet CH_3). Carbon magnetic resonance spectra were recorded on a Brüker DRX360 (90.0MHz), Brüker AV400 (100.0MHz) or Brüker DRX500 (500.1MHz) spectrometer, at ambient temperature, unless otherwise stated. All assignments were confirmed by ^1H–^{13}C HMQC and/or DEPT analysis.

The assignments of proton and carbon resonances shown in this Experimental followed from the aforementioned NMR experiments. Whilst the author is

reasonably confident that all the assignments are correct, some caution should be taken when two assignments are close in chemical shift.

Mass spectra were recorded on a VG Autospec MM-701CF or Micromass LCT spectrometer (CI^+ and EI^+). Only molecular ions and other significant peaks/fragments are reported. These instruments have a tolerance of ±10ppm and only formulae within ±10ppm are quoted. The required formulae are calculated using the most abundant isotopes of each element (*i.e.* ^{12}C, ^{1}H, ^{16}O, ^{14}N, ^{23}Na, all others as stated). All mass spectrometry data are high resolution and are quoted to 4 decimal places.

Microanalyses were performed by the Analytical Services Department in Nottingham. Results are quoted as percentages of the total mass and to the nearest 0.05%. Only data within 0.3% are quoted.

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer, as liquid films or as dilute solutions, in spectroscopic grade chloroform. Absorption maxima (ν_{max}) of major, significant peaks are reported in wavenumbers (cm^{-1}), quoted to the nearest integral wavenumber. The assignment of weak, medium, strong or broad is purely qualitative, based relative to the strongest C-H absorption peak.

Melting points were measured on a Kofler Hot-Stage or Bibby™ Stuart Scientific SMP3 melting point apparatus. The melting points are reported to the nearest ^{o}C and are uncorrected.

Thin Layer Chromatography (TLC) was carried out using Merck aluminium foil backed plates, pre-coated with Silica gel 60 F_{254} (1.05554.0001). Visualisation was effected *via* U.V fluorescence quenching (λ_{max}=254nm), using an iodine on silica dip, or staining with phosphomolybdic acid solution (12g phosphomolybdic acid in 250ml ethanol) or vanillin (12g 3-hydroxy-4-methoxybenzaldehyde, 2ml conc. sulphuric acid in 400ml ethanol), followed by heating. Flash column chromatography was performed using ICN Silica 32-63, 60Å employing the method of Still and co-workers.[114]

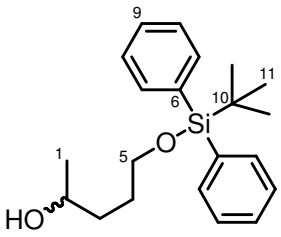
Anhydrous THF was obtained by distillation from sodium/benzophenone, under dry nitrogen, or *via* filtration through a nitrogen pressurised, basic, activated, 58Å aluminium oxide column. Anhydrous DCM was obtained by distillation from calcium hydride, under dry nitrogen. Anhydrous diethyl ether was obtained *via* filtration through a dry nitrogen pressurised, basic, activated, 58Å aluminium oxide column. Anhydrous benzene was obtained by distillation from sodium/benzophenone, under dry argon. Petrol refers to the fraction of light petroleum ether boiling between 40 and 60^{o}C. Evaporation of solvents was achieved using a Büchi rotavapor R-200.

Unless stated otherwise, reactions requiring anhydrous conditions were conducted in an inert atmosphere of dry nitrogen in flame-dried or oven-dried apparatus. Combined solvent extracts were dried over $MgSO_4$ prior to evaporation, unless stated otherwise. Lithium aluminium hydride reactions were quenched according to the method of Fieser and Fieser.[115] Triphenylphosphine was purified *by*

recrystallisation from hexane. IBX (2-iodoxybenzoic acid) was prepared according to the procedure of Santagostino.[116] The concentrations of basic alkylation reagents were determined by titration against 1,3-diphenylacetone *p*-tosylhydrazone. All other reagents used were purified according to C. L. L. Chai and W. L. F. Armarego "Purification of Laboratory Chemicals" Elsevier Science Plc, fifth edition, 2003, or used as they were supplied from commercial sources.

Experimental Details

***(±)-5-(tert-Butyl-diphenyl-silanyloxy)-pentan-2-ol* 126**

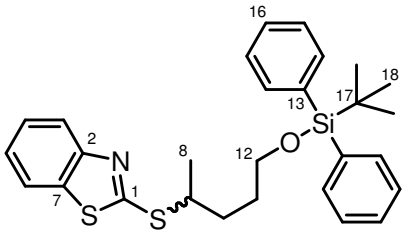


126

A solution of 1,4-pentanediol **125** (1.10g, 10.6mmol) in tetrahydrofuran (25ml) was added dropwise over 10 min, to a stirred suspension of sodium hydride (60% in mineral oil, 0.39g, 9.8mmol) (previously washed with pentane (3 x 25ml)) in tetrahydrofuran (50ml) at 0°C, under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min, and then *tert*-butyldiphenylsilyl chloride (2.50ml, 9.61mmol) was added dropwise, over 5 min at 0°C. The mixture was stirred at room temperature for 2 h, and then diethyl ether (20ml) and water (20ml) were added. The separated aqueous phase was extracted with diethyl ether (3 x 20ml) and the combined organic extracts were dried over sodium sulphate and then concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to give the silyl ether **126** (3.60g, 98%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3617 (s), 3418 (br s), 1067 (s); δ_H (400MHz,

$CDCl_3$), 1.07 (9H, s, $SiC(CH_3)_3$, *H*-11), 1.20 (3H, d, *J* 6.0Hz, $CH(OH)CH_3$, *H*-1), 1.27 (1H, br s, O*H*), 1.48-1.70 (4H, m, CH_2CH_2, *H*-3,4), 3.70 (2H, t, *J* 6.0Hz, $SiOCH_2$, *H*-5), 3.84 (1H, tq, *J* 7.0 and 6.0Hz, HOC*H*, *H*-2), 7.40-7.46 (6H, m, 6 x Ar*H*, *H*-8,9), 7.70-7.72 (4H, m, 4 x Ar*H*, *H*-7); δ_C (100MHz, $CDCl_3$), 19.1 (s, *C*-10), 23.4 (q, *C*-1), 26.8 (q, *C*-11), 28.9 (t, *C*-4), 36.2 (t, *C*-3), 64.2 (t, *C*-5), 67.8 (d, *C*-2), 127.6 (d, *C*-8), 129.6 (d, *C*-9), 133.6 (s, *C*-6), 135.6 (d, *C*-7); m/z (ES) 365.1945 ($M + Na^+$, $C_{21}H_{30}O_2{}^{28}SiNa$ requires 365.1913).

***(±)-2-[4-(tert-Butyl-diphenyl-silanyloxy)-1-methyl-butylsulfanyl]-benzothiazole* 127**

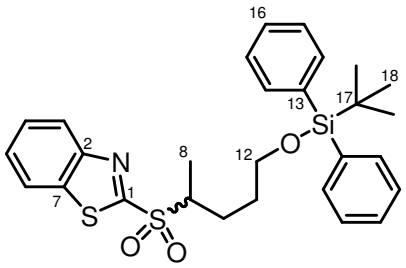


127

2-Mercaptobenzothiazole (0.74g, 4.4mmol) and triphenylphosphine (1.23g, 4.7mmol) were added sequentially, to a stirred solution of the alcohol **126** (1.0g, 2.9mmol) in tetrahydrofuran (33ml) at 0°C, under a nitrogen atmosphere. The mixture was stirred at 0°C for 5 min, and then diethyl azodicarboxylate (0.80ml, 4.4mmol) was added dropwise over 15 min. The yellow mixture was stirred at room temperature for 24h and then diethyl ether (6ml), water (6ml) and saturated aqueous brine (8ml) were added. The separated aqueous phase was extracted with diethyl ether (3 x 50ml) and the combined organic extracts were dried over sodium sulphate and then concentrated *in vacuo*. The residue was purified by flash column chromatography (5% Et_2O, 95% petrol) on silica gel, to give the sulphide **127** (1.44g, 99%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1111 (s); δ_H (400MHz,

$CDCl_3$), 1.04 (9H, s, SiC(CH_3)$_3$, *H*-18), 1.51 (3H, d, *J* 7.0Hz, SCHCH_3, *H*-8), 1.73-1.79 (2H, m, SiOCH_2CH_2, *H*-11), 1.83-1.91 (2H, m, SCHCH_2, *H*-10), 3.71 (2H, t, *J* 5.5Hz, SiOCH_2, *H*-12), 4.00 (1H, tq, *J* 7.0 and 6.5Hz, SC*H*, *H*-9), 7.28-7.44 (8H, m, 8 x Ar*H*, *H*-4,5,15,16), 7.66 (4H, dd, *J* 7.5 and 1.5Hz, 4 x Ar*H*, *H*-14), 7.75 (1H, dd, *J* 8.0 and 0.5Hz, Ar*H*, *H*-6), 7.86 (1H, app d, *J* 8.0Hz, Ar*H*, *H*-3); δ_C (100MHz, $CDCl_3$), 19.2 (s, *C*-17), 21.5 (q, *C*-8), 26.9 (q, *C*-18), 29.9 (t, *C*-11), 33.2 (t, *C*-10), 44.4 (d, *C*-9), 63.5 (t, *C*-12), 120.9 (d, *C*-6), 121.5 (d, *C*-3), 124.2 (d, *C*-4), 126.0 (d, *C*-5), 127.7 (d, *C*-15), 129.6 (d, *C*-16), 135.6 (d, *C*-14), 135.3, 137.2 (2 x s, *C*-7,13), 153.4 (s, *C*-2), 166.6 (s, *C*-1); m/z (ES) 492.1840 (M + H^+, $C_{29}H_{33}NO^{32}S_2{}^{28}Si$ requires 492.1851).

(±)-2-[5-(tert-Butyl-diphenyl-silanyloxy)-pentane-2-sulfonyl]-benzothiazole **122**

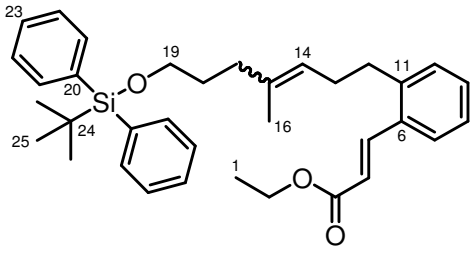


122

Saturated aqueous brine (20ml) was added to a solution of 3-chloroperoxybenzoic acid (70-75% in H_2O, 34.0g, 138mmol) in dichloromethane (50ml) at room temperature. The separated organic phase was then added dropwise, over 10 min, to a stirred solution of the sulphide **127** (30g, 60mmol) and sodium hydrogen carbonate (24.0g, 290mmol) in dichloromethane (150ml), at -40^{o}C. The stirred mixture was allowed to warm to room temperature over 12 h, and then dichloromethane (100ml) and saturated aqueous sodium thiosulphate solution (200ml) were added. The separated aqueous phase was extracted with dichloromethane (3 x 50ml) and the combined organic extracts were then washed

with water (5 x 200ml) and brine (5 x 100ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to give the sulfone **122** (29.9g, 93%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1147 (m), 1112 (s); δ_H (400MHz, $CDCl_3$), 0.96 (9H, s, $SiC(CH_3)_3$, *H*-18), 1.45 (3H, d, *J* 7.0Hz, $CHCH_3$, *H*-8), 1.44-1.64 (2H, m, $CH_2CH_2OTBDPS$, *H*-11), 1.68-1.78 (2H, m, $CH_2CH_2CH_2OTBDPS$, *H*-10), 3.65 (2H, t, *J* 6.0Hz, $CH_2OTBDPS$, *H*-12), 3.66 (1H, app t, *J* 7.0Hz, $CHCH_3$, *H*-9), 7.33-7.43 (6H, m, 6 x Ar*H,* *H*-15,16), 7.57-7.65 (6H, m, 6 x Ar*H,* *H*-4,5,14), 8.01 (1H, ddd, *J* 7.5, 1.0, and 0.5Hz, Ar*H,* *H*-6), 8.21 (1H, ddd, *J* 8.0, 1.0, 0.5Hz, Ar*H,* *H*-3); δ_C (100MHz, $CDCl_3$), 12.8 (q, *C*-8), 19.0 (s, *C*-17), 25.9 (t, *C*-10), 26.7 (q, *C*-18), 29.2 (t, *C*-11), 59.6 (d, *C*-9), 63.0 (t, *C*-12), 122.2 (d, *C*-3), 125.5 (d, *C*-6), 127.5 (d, *C*-4), 127.7 (d, *C*-15), 129.9 (d, *C*-5), 129.6 (d, *C*-16), 133.5, 136.9 (2 x s, *C*-7,13), 135.5 (d, *C*-14), 153.0 (s, *C*-2), 165.1 (s, *C*-1); m/z (ES) 546.1571 ($M + Na^+$, $C_{28}H_{33}NO_3{}^{32}S_2{}^{28}SiNa$ requires 546.1569).

***(2E)-Ethyl 3-(2-(7-(tert-Butyl-diphenyl-silanyloxy)-4-methylhept-3-enyl)phenyl)acrylate* 120a**



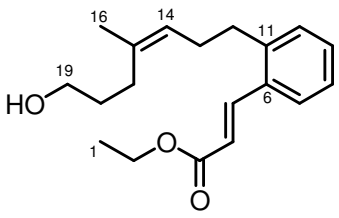
120a

Sodium hexamethyldisilazane (2.0M in THF, 1.7ml, 3.4mmol) was added dropwise over 10 min, to a stirred solution of the sulfone **122** (1.6g, 3.0mmol) in tetrahydrofuran (24ml) at -78°C, under a nitrogen atmosphere. The yellow solution was stirred at -78°C for 45 min and then a solution of the aldehyde **121a** (0.62g,

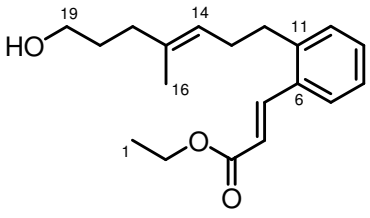
2.7mmol)[71] in tetrahydrofuran, (12ml) was added dropwise over 30 min. The mixture was stirred at -78°C for 2h and then allowed to warm to room temperature over 12h. Saturated aqueous ammonium chloride solution (10ml) was added, and the separated aqueous phase was then extracted with diethyl ether (3 x 50ml). The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOAc, 95% petrol) on silica gel, to give a 2:3 mixture of *Z* and *E* isomers of the alkene **120a** (0.42g, 38%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1703 (s), 1634 (s); δ_H (400MHz, $CDCl_3$), 1.05 (9H, 2 x s, $SiC(CH_3)_3$, *H*-25), 1.33 (3H, m, OCH_2CH_3, *H*-1), 1.44 (3H, s, $CH{=}CCH_3$, *H*-16), 1.47-1.67 (2H, m, CH_2CH_2OTBDPS, *H*-18), 1.98-2.10 (2H, m, $CH_2CH_2CH_2$OTBDPS, *H*-17), 2.18-2.34 (2H, m, $ArCH_2CH_2$, *H*-13), 2.71-2.82 (2H, m, $ArCH_2$, *H*-12), 3.57-3.67 (2H, m, CH_2OTBDPS, *H*-19), 4.25 (2H, 2 x q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.16 (1H, 2 x t, *J* 7.0Hz, $CH{=}CCH_3$, *H*-14), 6.35 (1H, 2 x d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 7.13-7.30 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.32-7.45 (6H, m, 6 x ArH, *H*-22,23), 7.54 (1H, 2 x dd, *J* 7.0 and 1.0Hz, Ar*H*, *H*-7), 7.62-7.70 (4H, m, 4 x Ar*H*, *H*-21), 8.01 (1H, 2 x d, *J* 16.0Hz, Ar*H*, *H*-5); δ_C (100MHz, $CDCl_3$), 14.3 (q, *C*-1), 15.8 (s, *C*-24), 19.1, 19.2 (2 x q, *C*-16), 26.8, 26.9 (2 x q, *C*-25), 29.7, 30.0 (2 x t, *C*-13), 30.3, 30.8 (2 x t, *C*-12), 33.4, 33.5 (2 x t, *C*-18), 34.4, 35.7 (2 x t, *C*-17), 60.4, 60.5 (2 x t, *C*-2), 63.3, 63.6 (2 x t, *C*-19), 119.2, 119.3 (2 x d, *C*-4), 122.9 (d, *C*-14), 126.4, 126.5 (2 x d, *C*-8), 127.5 (2C d, *C*-22), 129.5 (d, *C*-23), 129.9, 130.1, 130.9 (3 x d, *C*-8,9,10), 132.9, 133.0 (2 x s, *C*-20), 134.0, 134.1 (2 x s, *C*-6), 135.5, 135.6 (2 x 2C d, *C*-21), 136.0, 136.1 (2 x s, *C*-11), 138.0, 138.1 (2 x s, *C*-15), 141.9, 142.1 (2 x d, *C*-5), 167.0 (s, *C*-3); m/z (ES) 483.2349 (M^+ - ^tBu, $C_{31}H_{35}O_3{}^{28}Si$ requires 483.2355).

(2E)-Ethyl 3-(2-((Z)-7-hydroxy-4-methylhept-3-enyl)phenyl)acrylate **131a** ***and***

(2E)-ethyl 3-(2-((E)-7-hydroxy-4-methylhept-3-enyl)phenyl)acrylate **131b**



131a

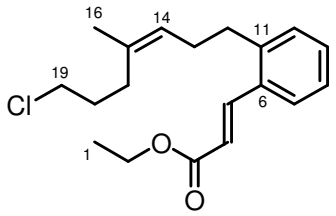


131b

A solution of tetra-*n*-butylammonium fluoride (0.16g, 0.5mmol) in tetrahydrofuran (1ml) was added dropwise over 10 min, to a stirred solution of the silyl ether **120a** (0.12g, 0.3mmol) in tetrahydrofuran (2ml) at 0^{o}C, under a nitrogen atmosphere. The pink solution was allowed to warm to room temperature over 3 h and then diethyl ether (2ml) and water (2ml) were added dropwise. The separated aqueous phase was extracted with diethyl ether (3 x 30ml) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to give: i) the *Z*-isomer of the alcohol **131a** (0.021g, 25%) (eluted first) as a colourless oil; (Found C, 71.2; H, 7.9%. $C_{19}H_{25}ClO_2$ requires C, 71.1; H, 7.9%); ν_{max}(sol $CHCl_3$)/cm^{-1}, 3623 (br m), 1706 (s), 1633 (s); δ_H (400MHz, $CDCl_3$), 1.26 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.53 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2OH, *H*-18), 1.62 (3H, s, $CH{=}CCH_3$, *H*-16), 1.90 (1H, br s, O*H*), 2.00 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2OH$, *H*-17), 2.20 (2H, dt, *J* 8.0 and 7.5Hz, $ArCH_2CH_2$, *H*-13), 2.70 (2H, td, *J* 8.0 and 1.0Hz, $ArCH_2$, *H*-12), 3.52 (2H, t, *J* 6.5Hz, CH_2OH, *H*-19), 4.19 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.16 (1H, app t, *J* 7.5Hz, $CH{=}CCH_3$, *H*-14), 6.30 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 7.19 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.50 (1H, dd, *J* 7.0 and 2.0Hz, Ar*H*, *H*-7), 7.99 (1H, d, *J* 16.0Hz, ArCH=CH, *H*-5); nOe enhancement between H-13 and H-17 of 3%; δ_C (100MHz, $CDCl_3$), 14.3 (q, *C*-1), 23.3 (q, *C*-16), 28.0 (t, *C*-13),

30.4 (t, *C*-12), 31.0 (t, *C*-18), 34.0 (t, *C*-17), 60.7 (t, *C*-2), 62.4 (t, *C*-19), 119.1 (d, *C*-4), 124.3 (d, *C*-14), 126.4 (d, *C*-8), 129.0 (d, *C*-7), 130.1, 130.3 (2 x d, *C*-9,10), 132.9 (s, *C*-6), 136.0 (s, *C*-11), 142.1 (s, *C*-15), 142.5 (d, *C*-5), 167.2 (s, *C*-3); m/z (ES) 325.1793 ($M + Na^+$, $C_{19}H_{26}O_3Na$ requires 325.1779); and ii) the *E*-isomer of the alcohol **131b** (0.045g, 52%) (eluted second) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3623 (br w), 1706 (s), 1633 (s); δ_H (400MHz, $CDCl_3$), 1.34 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.52 (4H, br s, $CH=CCH_3$ + O*H*, *H*-16), 1.64 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2OH, *H*-18), 2.03 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2OH$, *H*-17), 2.27 (2H, dt, *J* 7.5 and 7.0Hz, $ArCH_2CH_2$, *H*-13), 2.78 (2H, t, *J* 7.5Hz, $ArCH_2$, *H*-12), 3.60 (2H, t, *J* 6.5Hz, CH_2OH, *H*-19), 4.27 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.21 (1H, t, *J* 7.0Hz, $CH=CCH_3$, *H*-14), 6.36 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 7.18-7.32 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.56 (1H, app d, *J* 7.5Hz, Ar*H*, *H*-7), 8.02 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); nOe enhancement between H-13 and H-16 of 2%; δ_C (100MHz, $CDCl_3$), 14.3 (q, *C*-1), 15.8 (q, *C*-16), 29.9 (t, *C*-13), 30.7 (t, *C*-12), 33.3 (t, *C*-18), 35.8 (t, *C*-17), 60.5 (t, *C*-2), 62.7 (t, *C*-19), 119.3 (d, *C*-4), 123.3 (d, *C*-14), 126.4, 126.5 (2 x d, *C*-7,8), 129.9, 130.2 (2 x d, *C*-9,10), 133.0 (s, *C*-6), 136.0 (s, *C*-11), 141.8 (s, *C*-15), 142.3 (d, *C*-5), 167.1 (s, *C*-3); m/z (ES) 325.1764 ($M + Na^+$, $C_{19}H_{26}O_3Na$ requires 325.1779).

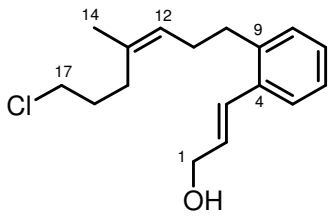
(2E)-Ethyl 3-(2-((Z)-7-chloro-4-methylhept-3-enyl)phenyl)acrylate **132a**



132a

N-Chlorosuccinimide (69mg, 0.52mmol) was added in one portion, to a stirred solution of the *Z*-alcohol **131a** (105mg, 0.35mmol), triphenylphosphine (120mg, 0.47mmol) and potassium carbonate (19mg, 0.14mmol) in dichloromethane (10ml) at 0°C, under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O, 90% petrol) on silica gel, to give the chloride **132a** (110mg, 96%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1706 (s), 1633 (s); δ_H (400MHz, $CDCl_3$), 1.28 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.59 (3H, d, *J* 1.0Hz, $CH{=}CCH_3$, *H*-16), 1.64 (2H, tt, *J* 7.0 and 6.5Hz, CH_2CH_2Cl, *H*-18), 2.01 (2H, t, *J* 7.0Hz, $CH_2CH_2CH_2Cl$, *H*-17), 2.20 (2H, dt, *J* 7.5 and 7.0Hz, $ArCH_2CH_2$, *H*-13), 2.72 (2H, t, *J* 7.0Hz, $ArCH_2$, *H*-12), 3.36 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-19), 4.20 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.17 (1H, app t, *J* 7.5Hz, $CH{=}CCH_3$, *H*-14), 6.29 (1H, d, *J* 16.0Hz, ArCH=CH, *H*-4), 7.20-7.35 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.48 (1H, dd, *J* 7.5 and 1.0Hz, Ar*H*, *H*-7), 7.94 (1H, d, *J* 16.0Hz, $ArCH{=}CH$, *H*-5); δ_C (100MHz, $CDCl_3$), 11.6 (q, *C*-1), 14.4 (q, *C*-16), 30.2, 30.8 (2 x t, *C*-13,18), 35.0 (t, *C*-12), 38.2 (t, *C*-17), 44.4 (t, *C*-19), 60.6 (t, *C*-2), 120.2 (d, *C*-4), 125.2 (d, *C*-14), 126.8, 127.0 (2 x d, *C*-7,8), 130.1, 130.3 (2 x d, *C*-9,10), 133.1 (s, *C*-6), 137.5 (s, *C*-11), 140.1 (s, *C*-15), 141.5 (d, *C*-5), 166.8 (s, *C*-3); m/z (ES) 321.1598 ($M + H^+$, $C_{19}H_{26}{}^{35}ClO_2$ requires 321.1621).

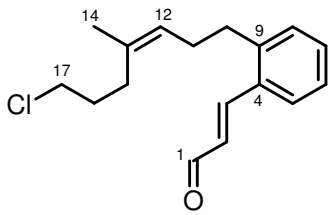
(2E)-3-(2-((Z)-7-Chloro-4-methylhept-3-enyl)phenyl)prop-2-en-1-ol **133a**



133a

Diisobutylaluminium hydride (1.0M in hexanes, 6.3ml, 6.3mmol) was added dropwise over 10 min, to a stirred solution of the *Z*-ester **132a** (0.96g, 3.0mmol) in dichloromethane (50ml) at -78^{o}C under a nitrogen atmosphere. The mixture was stirred at -78^{o}C for 4h and then saturated aqueous Rochelle's salt (50ml) was added at 0^{o}C. The separated aqueous phase was extracted with dichloromethane (3 x 100ml) and the combined organic extracts were dried and then concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel to give the *Z*-alcohol **133a** (0.72g, 86%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3611 (br m), 1600 (w); δ_H (400MHz, $CDCl_3$), 1.69 (3H, s, CH=CCH_3, *H*-14), 1.77 (2H, m, CH_2CH_2Cl, *H*-16), 2.12 (2H, t, *J* 7.5Hz, CH_2CH_2CH_2Cl, *H*-15), 2.30 (2H, dt, *J* 8.0 and 7.0Hz, ArCH_2CH_2, *H*-11), 2.73 (2H, t, *J* 8.0Hz, ArCH_2, *H*-10), 3.47 (2H, t, *J* 7.0Hz, CH_2Cl, *H*-17), 4.35 (2H, dd, *J* 6.0 and 1.0Hz, CH_2OH, *H*-1), 5.28 (1H, t, *J* 7.0Hz, C*H*=CCH_3, *H*-12), 6.28 (1H, dt, *J* 16.0 and 6.0Hz, ArCH=C*H*, *H*-2), 6.90 (1H, app d, *J* 16.0Hz, ArC*H*=CH, *H*-3), 7.14-7.25 (3H, m, 3 x Ar*H*, *H*-6,7,8), 7.47 (1H, dd, *J* 6.0 and 2.5Hz, Ar*H*, *H*-5); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-14), 28.9 (t, *C*-11), 29.4 (t, *C*-10), 30.8 (t, *C*-16), 33.6 (t, *C*-15), 44.8 (t, *C*-17), 63.9 (t, *C*-1), 125.6, 126.2, 126.3, 127.7, 128.7, 129.7, 130.2 (7 x d, *C*-2,3,5,6,7,8,12), 134.3 (s, *C*-4), 135.4 (s, *C*-9), 139.6 (s, *C*-13); m/z (ES) 301.1342 (M + Na^+, $C_{17}H_{23}{}^{35}ClONa$ requires 301.1335).

(2E)-3-(2-((Z)-7-Chloro-4-methylhept-3-enyl)phenyl)acrylaldehyde **134a**

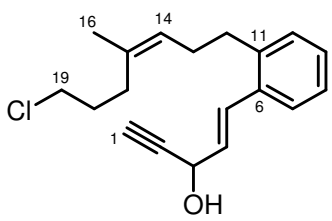


134a

Activated manganese (IV) oxide (4.34g, 50.5mmol) was added portionwise over 5 mins, to a stirred solution of the *Z*-alcohol **133a** (0.70g, 2.5mmol) in dichloromethane (50ml) at room temperature, under a nitrogen atmosphere. The mixture was stirred at room temperature for 21h, then filtered through celite with ethyl acetate (200ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to give the *Z*-aldehyde **134a** (0.62g, 89%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1673 (s), 1622 (m); δ_H (400MHz, $CDCl_3$), 1.68 (3H, d, *J* 1.0Hz, CH=CC*H*$_3$, *H*-14), 1.74 (2H, m, C*H*$_2$CH$_2$Cl, *H*-16), 2.10 (2H, t, *J* 7.5Hz, C*H*$_2$CH$_2$CH$_2$Cl, *H*-15), 2.36 (2H, dt, *J* 7.5 and 7.0Hz, ArCH$_2$C*H*$_2$, *H*-11), 2.86 (2H, t, *J* 7.5Hz, ArC*H*$_2$, *H*-10), 3.45 (2H, t, *J* 6.5Hz, C*H*$_2$Cl, *H*-17), 5.26 (1H, app t, *J* 7.0Hz, C*H*=CCH$_3$, *H*-12), 6.70 (1H, dd, *J* 16.0 and 7.5Hz, ArCH=C*H*, *H*-2), 7.25-7.33 (2H, m, 2 x Ar*H*, *H*-6,8), 7.39 (1H, ddd, *J* 7.5, 7.0 and 1.0Hz, Ar*H*, *H*-7), 7.62 (1H, dd, *J* 8.0 and 1.0Hz, Ar*H*, *H*-5), 7.85 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-3), 9.76 (1H, d, *J* 7.5Hz, C(O)*H*, *H*-1); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-14), 28.7 (t, *C*-11), 30.0 (t, *C*-10), 30.6 (t, *C*-16), 33.5 (t, *C*-15), 44.6 (t, *C*-17), 124.9 (d, *C*-12), 126.8, 126.9 (2 x d, *C*-5,6), 129.6 (d, *C*-7), 130.5 (d, *C*-8), 131.1 (d, *C*-2), 132.4 (s, *C*-4), 134.9 (s, *C*-9), 142.1 (s, *C*-13), 150.1 (d, *C*-3), 193.8 (d, *C*-1); m/z (ES) 277.1335 ($M + H^+$, $C_{17}H_{22}{}^{35}ClO$ requires 277.1359).

(±)-(1E)-1-(2-((Z)-7-Chloro-4-methylhept-3-enyl)phenyl)pent-1-en-4-yn-3-ol

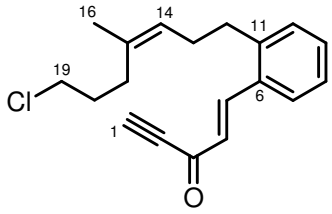
135a



135a

Ethynylmagnesium bromide (0.5M in THF, 0.64ml, 0.32mmol) was added dropwise over 5 min, to a stirred solution of the *Z*-aldehyde **134a** (59mg, 0.21mmol) in tetrahydrofuran (5ml) at -78^{o}C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature over 22h, and then diethyl ether (5ml) and saturated aqueous ammonium chloride (5ml) were added. The separated aqueous phase was extracted with diethyl ether (3 x 25ml) and the combined organic extracts were then washed with brine (20ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to give the *Z*-propargylic alcohol **135a** (64mg, 98%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3594 (m), 3305 (s), 1601 (w); δ_H (400MHz, $CDCl_3$), 1.44 (3H, s, CH=CC*H*$_3$, *H*-16), 1.79 (2H, tt, *J* 7.5 and 7.0Hz, C*H*$_2$CH$_2$Cl, *H*-18), 1.94 (1H, d, *J* 6.0Hz, O*H*), 2.04 (2H, t, *J* 7.5Hz, C*H*$_2$CH$_2$CH$_2$Cl, *H*-17), 2.19 (2H, dt, *J* 7.5 and 7.0Hz, ArCH$_2$C*H*$_2$, *H*-13), 2.58 (1H, t, *J* 2.0Hz, ≡C-*H*, *H*-1), 2.66 (2H, t, *J* 7.5Hz, ArC*H*$_2$, *H*-12), 3.41 (2H, t, *J* 7.0Hz, C*H*$_2$Cl, *H*-19), 4.99-5.05 (1H, m, C*H*OH, *H*-3), 5.15 (1H, t, *J* 7.0Hz, C*H*=CCH$_3$, *H*-14), 6.13 (1H, dd, *J* 15.5 and 6.0Hz, ArCH=C*H*, *H*-4), 7.02-7.20 (4H, m, ArC*H*=CH + 3 x Ar*H*, *H*-5,8,9,10), 7.38 (1H, dd, *J* 7.0 and 1.5Hz, Ar*H*, *H*-7); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-16), 28.9 (t, *C*-13), 29.5 (t, *C*-12), 30.7 (t, *C*-18), 33.6 (t, *C*-17), 44.8 (t, *C*-19), 63.0 (d, *C*-3), 74.6 (d, *C*-1), 83.2 (s, *C*-2), 125.5, 126.2, 126.4, 128.1, 129.0, 129.8, 130.0 (7 x d, *C*-4,5,7,8,9,10,14), 134.3, 134.5 (2 x s, *C*-6,11), 140.0 (s, *C*-15); m/z (ES) 325.1355 (M + Na$^+$, $C_{19}H_{23}{}^{35}ClONa$ requires 325.1335).

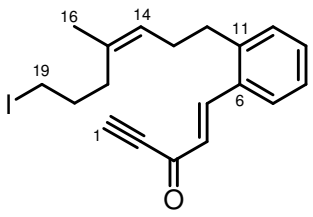
(1E)-1-(2-((Z)-7-Chloro-4-methylhept-3-enyl)phenyl)pent-1-en-4-yn-3-one **136a**



136a

Activated manganese (IV) oxide (290mg, 3.3mmol) was added portionwise over 5 mins, to a stirred solution of the *Z*-secondary alcohol **135a** (50mg, 0.2mmol) in dichloromethane (5ml) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 18h, then filtered through celite with dichloromethane (50ml) and warm ethyl acetate (50ml), and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to give the *Z*-acetylenic ketone **136a** (40mg, 81%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3297 (m), 2101 (m), 1635 (s), 1598 (m); δ_H (400MHz, $CDCl_3$), 1.65 (3H, d, *J* 1.0Hz, CH=CC*H*$_3$, *H*-16), 1.70 (2H, tt, *J* 7.5 and 6.5Hz, C*H*$_2$CH$_2$Cl, *H*-18), 2.04 (2H, t, *J* 7.5Hz, C*H*$_2$CH$_2$CH$_2$Cl, *H*-17), 2.32 (2H, dt, *J* 7.5 and 7.0Hz, ArCH$_2$C*H*$_2$, *H*-13), 2.83 (2H, t, *J* 7.5Hz, ArC*H*$_2$, *H*-12), 3.34 (1H, s, ≡C-*H*, *H*-1), 3.40 (2H, t, *J* 6.5Hz, C*H*$_2$Cl, *H*-19), 5.23 (1H, app t, *J* 7.0Hz, C*H*=CCH$_3$, *H*-14), 6.75 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 7.21-7.32 (2H, m, 2 x Ar*H*, *H*-8,10), 7.37 (1H, ddd, *J* 7.5, 7.0 and 1.5Hz, Ar*H*, *H*-9), 7.60 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-7), 8.26 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-16), 28.8 (t, *C*-12), 30.1 (t, *C*-13), 30.6 (t, *C*-18), 33.5 (t, *C*-17), 44.6 (t, *C*-19), 79.1 (d, *C*-1), 80.1 (s, *C*-2), 124.7 (d, *C*-14), 126.7 (d, *C*-8), 128.6 (d, *C*-7), 130.2, 130.5, 131.2 (3 x d, *C*-4,9,10), 132.3 (s, *C*-6), 135.0 (s, *C*-11), 142.6 (s, *C*-15), 147.2 (d, *C*-5), 177.6 (s, *C*-3); m/z (ES) 301.1367 (M + H^+, $C_{19}H_{22}{}^{35}ClO$ requires 301.1359).

(1E)-1-(2-((Z)-7-Iodo-4-methylhept-3-enyl)phenyl)pent-1-en-4-yn-3-one **117a**

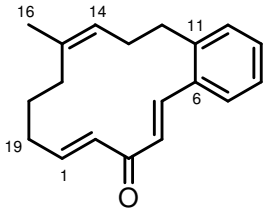


117a

Sodium iodide (220mg, 1.5mmol) was added in one portion, to a stirred solution of the *Z*- chloride **136a** (115mg, 0.4mmol) and potassium carbonate (2mg, 0.01mmol) in 2-butanone (6ml) at room temperature under a nitrogen atmosphere. The mixture was heated under reflux for 24h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O, 90% petrol) on silica gel to give the iodide **117a** (129mg, 87%) as a yellow oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3297 (s), 2102 (s), 1635 (s), 1598 (s); δ_H (400MHz, $CDCl_3$), 1.64 (3H, s, CH=CCH_3, *H*-16), 1.74 (2H, tt, *J* 7.5 and 7.0Hz, CH_2CH_2I, *H*-18), 1.97 (2H, t, *J* 7.5Hz, CH_2CH_2CH_2I, *H*-17), 2.33 (2H, dt, *J* 7.5 and 7.5Hz, ArCH_2CH_2, *H*-13), 2.84 (2H, t, *J* 7.5Hz, ArCH_2, *H*-12), 3.04 (2H, t, *J* 7.0Hz, CH_2I, *H*-19), 3.34 (1H, s, ≡C-*H*, *H*-1), 5.22 (1H, t, *J* 7.5Hz, C*H*=CCH_3, *H*-14), 6.75 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 7.22-7.29 (2H, m, 2 x Ar*H*, *H*-8,10), 7.37 (1H, ddd, *J* 7.5, 7.0 and 1.5Hz, Ar*H*, *H*-9), 7.60 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-7), 8.26 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 6.5 (t, *C*-19), 23.3 (q, *C*-16), 30.2, (t, *C*-13), 31.7 (t, *C*-18), 32.4 (t, *C*-12), 33.6 (t, *C*-17), 79.2 (d, *C*-1), 80.2 (s, *C*-2), 124.8 (d, *C*-14), 126.8, 126.9 (2 x d, *C*-7,8), 128.7 (d, *C*-4), 130.6 (d, *C*-10), 131.2 (d, *C*-9), 132.3 (s, *C*-6), 134.9 (s, *C*-11), 142.6 (s, *C*-15), 147.3 (d, *C*-5), 177.7 (s, *C*-3); m/z (ES) 393.0742 ($M + H^+$, $C_{19}H_{22}{}^{127}IO$ requires 393.0715).

(5E,8E,13Z)-11,12,15,16-Tetrahydro-13-methylbenzo[14]annulen-7(10H)-one

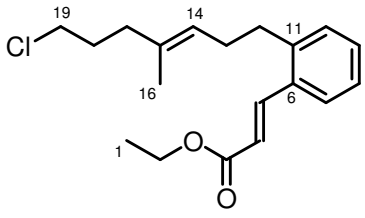
137a



137a

A solution of tri-*n*-butyltin hydride (110µl, 0.41mmol) and 2,2'-azobis(isobutyronitrile) (32mg, 0.19mmol) in degassed benzene (13ml) was added dropwise, over 8 h, *via* syringe pump to a stirred solution of the iodide **117a** (127mg, 0.32mmol) and 2,2'-azobis(isobutyronitrile) (16mg, 0.10mmol) in degassed benzene (130ml) at 80°C under an argon atmosphere. The mixture was heated under reflux for a further 12h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (5–10% Et_2O, 95-90% petrol) on silica gel to leave the macrocycle **137a** (30mg, 35%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1644 (s), 1623 (s); δ_H (400MHz, $CDCl_3$), 1.63-1.76 (2H, m, CH=CHCH$_2$CH_2, *H*-18), 1.76 (3H, s, CH=CCH_3, *H*-16), 2.12-2.20 (4H, m, ArCH$_2$CH_2 + CH=CHCH$_2$CH$_2$CH_2, *H*-13,17), 2.37 (2H, dtd, *J* 7.0, 4.5 and 1.5Hz, CH=CHCH_2, *H*-19), 2.66 (1H, app dd, *J* 5.0 and 4.0Hz, ArCH_aH$_b$, *H*-12$_a$), 2.67 (1H, app d, *J* 12.0Hz, ArCH$_a$$H_b$, *H*-12$_b$), 5.37 (1H, t, *J* 8.0Hz, C*H*=CCH$_3$, *H*-14), 6.21 (1H, dt, *J* 16.0 and 1.5Hz, O=CC*H*=CH, *H*-2), 6.58 (1H, dt, *J* 16.0 and 4.5Hz, O=CCH=C*H*, *H*-1), 6.73 (1H, d, *J* 16.5Hz, ArCH=C*H*, *H*-4), 6.97-7.34 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.70 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-7), 7.86 (1H, d, *J* 16.5Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-16), 28.1 (t, *C*-18), 30.1, 31.3 (2 x t, *C*-13,17), 32.1 (t, *C*-19), 35.3 (t, *C*-12), 123.4 (d, *C*-14), 125.7 (d, *C*-8), 126.9 (d, *C*-7), 127.7 (d, *C*-10), 130.5, 130.6, 130.7 (3 x d, *C*-2,4,9), 132.3 (s, *C*-15), 137.7 (s, *C*-6), 142.2 (s, *C*-11), 142.7 (d, *C*-5), 147.7 (d, *C*-1), 197.0 (s, *C*-3); m/z (ES) 289.1566 (M + Na^+, $C_{19}H_{22}ONa$ requires 289.1568).

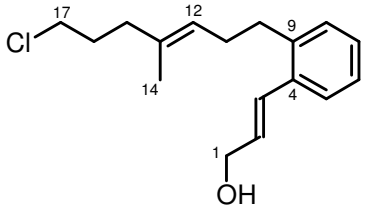
(2E)-Ethyl 3-(2-((E)-7-chloro-4-methylhept-3-enyl)phenyl)acrylate **132b**



132b

N-Chlorosuccinimide (0.067g, 0.50mmol) was added in one portion, to a stirred solution of the alcohol **131b** (0.115g, 0.38mmol), triphenylphosphine (0.117g, 0.45mmol) and potassium carbonate (12mg, 0.15mmol) in dichloromethane (5ml) at 0^{o}C, under a nitrogen atmosphere. The mixture was stirred at room temperature for 1h and then concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O, 90% petrol) on silica gel, to leave the chloride **132b** (0.119g, 98%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1706 (s), 1633 (s); δ_H (400MHz, $CDCl_3$), 1.35 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.50 (3H, app s, $CH{=}CCH_3$, *H*-16), 1.83 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2Cl, *H*-18), 2.09 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2Cl$, *H*-17), 2.27 (2H, dt, *J* 7.5 and 7.0Hz, $ArCH_2CH_2$, *H*-13), 2.79 (2H, t, *J* 7.0Hz, $ArCH_2$, *H*-12), 3.46 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-19), 4.27 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.22 (1H, tq, *J* 7.5 and 1.0Hz, $CH{=}CCH_3$, *H*-14), 6.37 (1H, d, *J* 16.0Hz, ArCH=CH, *H*-4), 7.16-7.36 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.56 (1H, app d, *J* 7.5Hz, Ar*H*, *H*-7), 8.02 (1H, d, *J* 16.0Hz, ArCH=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 14.3 (q, *C*-1), 15.7 (q, *C*-16), 29.9 (t, *C*-13), 30.6 (t, *C*-18), 33.3 (t, *C*-12), 36.6 (t, *C*-17), 44.6 (t, *C*-19), 60.5 (t, *C*-2), 119.3 (d, *C*-4), 124.1 (d, *C*-14), 126.5, 126.6 (2 x d, *C*-7,8), 129.9, 130.2 (2 x d, *C*-9,10), 133.0 (s, *C*-6), 134.6 (s, *C*-11), 141.7 (s, *C*-15), 142.1 (d, *C*-5), 167.0 (s, *C*-3); m/z (ES) 343.1430 (M + Na^+, $C_{19}H_{25}{}^{35}ClO_2Na$ requires 343.1435).

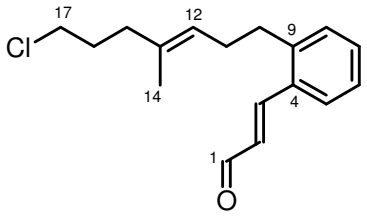
(2E)-3-(2-((E)-7-Chloro-4-methylhept-3-enyl)phenyl)prop-2-en-1-ol **133b**



133b

Diisobutylaluminium hydride (1.0M in hexanes, 8.25ml, 8.25mmol) was added dropwise over 10 min, to a stirred solution of the ester **132b** (1.26g, 3.93mmol) in dichloromethane (50ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 4h and then a saturated aqueous solution of Rochelle's salt (50ml) was added at 0°C. The aqueous phase was extracted with dichloromethane (3 x 100ml) and then the combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to leave the alcohol **133b** (0.93g, 85%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3609 (br s), 1601 (w); δ_H (400MHz, $CDCl_3$), 1.52 (3H, app s, CH=CCH_3, *H*-14), 1.84 (2H, tt, *J* 7.5 and 7.0Hz, CH_2CH_2Cl, *H*-16), 2.10 (2H, t, *J* 7.5Hz, CH_2CH_2CH_2Cl, *H*-15), 2.26 (2H, dt, *J* 8.0 and 7.5Hz, ArCH_2CH_2, *H*-11), 2.70 (2H, t, *J* 8.0Hz, ArCH_2CH_2, *H*-10), 3.47 (2H, t, *J* 7.0Hz, CH_2Cl, *H*-17), 4.36 (2H, dd, *J* 5.5 and 1.5Hz, ≡C-*H*, *H*-1), 5.23 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH_3, *H*-12), 6.27 (1H, dt, *J* 15.5 and 5.5Hz, ArCH=C*H*, *H*-2), 6.70 (1H, dt, *J* 15.5 and 1.5Hz, ArC*H*=CH, *H*-3), 7.11-7.23 (3H, m, 3 x Ar*H*, *H*-6,7,8), 7.46 (1H, dd, *J* 7.5 and 2.0Hz, Ar*H*, *H*-5); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-14), 28.7 (t, *C*-10), 29.6 (t, *C*-11), 32.3 (t, *C*-16), 36.6 (t, *C*-15), 44.7 (t, *C*-17), 63.9 (t, *C*-1), 124.7, 126.3, 126.4, 127.6, 129.7, 130.3, 130.9 (7 x d, *C*-2,3,5,6,7,8,12), 134.3 (s, *C*-4), 135.4 (s, *C*-9), 139.6 (s, *C*-13); m/z (ES) 301.1330 (M + Na^+, $C_{17}H_{23}{}^{35}ClONa$ requires 301.1335).

(2E)-3-(2-((E)-7-Chloro-4-methylhept-3-enyl)phenyl)acrylaldehyde **134b**

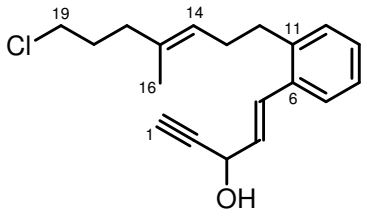


134b

Activated manganese (IV) oxide (1.21g, 13.9mmol) was added portionwise, to a stirred solution of the alcohol **133b** (0.18g, 0.6mmol) in dichloromethane (20ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 22h and then filtered through celite with dichloromethane (50ml), and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to leave the aldehyde **134b** (0.15g, 87%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1674 (s), 1621 (m); δ_H (400MHz, $CDCl_3$), 1.49 (3H, d, *J* 0.5Hz, CH=CC*H*$_3$, *H*-14), 1.83 (2H, tt, *J* 7.5 and 6.5Hz, C*H*$_2$CH$_2$Cl, *H*-16), 2.10 (2H, t, *J* 7.5Hz, C*H*$_2$CH$_2$CH$_2$Cl, *H*-15), 2.30 (2H, dt, *J* 7.5 and 7.0Hz, ArCH$_2$C*H*$_2$, *H*-11), 2.83 (2H, t, *J* 7.0Hz, ArC*H*$_2$, *H*-10), 3.46 (2H, t, *J* 6.5Hz, C*H*$_2$Cl, *H*-17), 5.22 (1H, tq, *J* 7.5 and 0.5Hz, C*H*=CCH$_3$, *H*-12), 6.69 (1H, dd, *J* 15.5 and 7.5Hz, ArCH=C*H*, *H*-2), 7.22-7.30 (2H, m, 2 x Ar*H*, *H*-6,8), 7.37 (1H, ddd, *J* 7.5, 7.0 and 1.5Hz, Ar*H*, *H*-7), 7.61 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-5), 7.82 (1H, d, *J* 15.5Hz, ArC*H*=CH, *H*-3), 9.74 (1H, d, *J* 7.5Hz, C(O)*H*, *H*-1); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-14), 30.0 (t, *C*-11), 30.6 (t, *C*-16), 33.3 (t, *C*-10), 36.6 (t, *C*-15), 44.5 (t, *C*-17), 123.9 (d, *C*-12), 126.8, 126.9 (2 x d, *C*-5,6), 129.7 (d, *C*-7), 130.5 (d, *C*-8), 131.0 (d, *C*-2), 132.4 (s, *C*-4), 135.0 (s, *C*-9), 142.1 (s, *C*-13), 150.1 (d, *C*-3), 193.8 (d, *C*-1); m/z (ES) 299.1195 (M + Na^+, $C_{17}H_{21}{}^{35}ClONa$ requires 299.1173).

(±)-(1E)-1-(2-((E)-7-Chloro-4-methylhept-3-enyl)phenyl)pent-1-en-4-yn-3-ol

135b

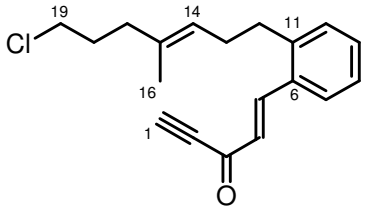


135b

Ethynylmagnesium bromide (0.5M in THF, 1.64ml, 0.82mmol) was added dropwise over 5 min, to a stirred solution of the aldehyde **134b** (0.15g, 0.55mmol) in tetrahydrofuran (10ml) at -78°C, under a nitrogen atmosphere. The solution was slowly warmed to room temperature over 22h and then diethyl ether (10ml) and a saturated aqueous ammonium chloride solution (10ml) were added. The aqueous phase was extracted with diethyl ether (3 x 25ml) and the combined organic extracts washed with brine (20ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to leave the alkyne **135a** (0.16g, 98%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3594 (m), 3305 (s), 1648 (w); δ_H (400MHz, $CDCl_3$), 1.51 (3H, app s, CH=CCH_3, *H*-16), 1.59 (1H, br s, O*H*), 1.83 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2Cl, *H*-18), 2.10 (2H, t, *J* 7.5Hz, C$H_2CH_2CH_2Cl$, *H*-17), 2.26 (2H, dt, *J* 7.5 and 7.0Hz, ArCH_2CH_2, *H*-13), 2.65 (1H, d, *J* 2.0Hz, ≡C-*H*, *H*-1), 2.71 (2H, t, *J* 7.5Hz, ArCH_2, *H*-12), 3.46 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-19), 5.06-5.12 (1H, m, C*H*OH, *H*-3), 5.23 (1H, tq, *J* 7.0 and 1.0Hz, C*H*=CCH_3, *H*-14), 6.21 (1H, dd, *J* 15.5 and 6.0Hz, ArCH=C*H*, *H*-4), 7.07-7.25 (4H, m, ArC*H*=CH + 3 x Ar*H*, *H*-5,8,9,10), 7.47 (1H, dd, *J* 7.0 and 2.0Hz, Ar*H*, *H*-7); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-16), 29.5 (t, *C*-13), 30.6 (t, *C*-12), 33.3 (t, *C*-18), 36.6 (t, *C*-17), 44.6 (t, *C*-19), 62.9 (d, *C*-3), 74.6 (d, *C*-1), 84.5 (s, *C*-2), 124.5, 126.2,

126.3, 128.1, 128.9, 129.7, 130.0 (7 x d, *C*-4,5,7,8,9,10,14), 134.3 134.6 (2 x s, *C*-6,11), 140.0 (s, *C*-15).

(1E)-1-(2-((E)-7-Chloro-4-methylhept-3-enyl)phenyl)pent-1-en-4-yn-3-one **136b**

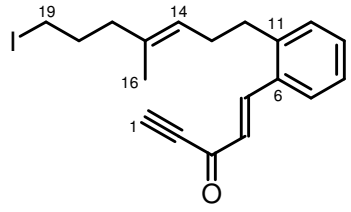


136b

Activated manganese (IV) oxide (0.95g, 10.9mmol) was added portionwise, to a stirred solution of the alcohol **135b** (0.14g, 0.5mmol) in dichloromethane (20ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 60h, filtered through celite with dichloromethane (50ml) and warm ethyl acetate (50ml), and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to leave the ketone **136b** (0.12g, 86%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3297 (m), 2101 (m), 1635 (s), 1598 (m); δ_H (400MHz, $CDCl_3$), 1.51 (3H, app s, CH=CC*H*$_3$, *H*-16), 1.83 (2H, m, C*H*$_2$CH$_2$Cl, *H*-18), 2.12 (2H, t, *J* 7.5Hz, C*H*$_2$CH$_2$CH$_2$Cl, *H*-17), 2.32 (2H, dt, *J* 7.5 and 7.0Hz, ArCH$_2$C*H*$_2$, *H*-13), 2.86 (2H, t, *J* 7.0Hz, ArC*H*$_2$, *H*-12), 3.35 (1H, s, ≡C-*H*, *H*-1), 3.47 (2H, t, *J* 6.5Hz, C*H*$_2$Cl, *H*-19), 5.24 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH$_3$, *H*-14), 6.77 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 7.21-7.31 (2H, m, 2 x Ar*H*, *H*-8,10), 7.39 (1H, ddd, *J* 7.5, 7.0 and 1.0Hz, Ar*H*, *H*-9), 7.62 (1H, dd, *J* 7.5 and 1.0Hz, Ar*H*, *H*-7), 8.28 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-16), 30.2 (t, *C*-12), 30.6 (t, *C*-13), 33.4 (t, *C*-18), 36.6 (t, *C*-17), 44.5 (t, *C*-19), 79.1 (d, *C*-1), 80.9 (s, *C*-2), 123.9 (d, *C*-14), 126.8 (d, *C*-8), 128.8 (d, *C*-7), 130.6, 131.0, 131.2 (3 x d, *C*-4,9,10), 132.6 (s, *C*-6), 134.9 (s, *C*-11),

142.3 (s, *C*-15), 147.2 (d, *C*-5), 172.9 (s, *C*-3); m/z (ES) 323.1173 ($M + Na^+$, $C_{19}H_{21}{}^{35}ClONa$ requires 323.1173).

(1E)-1-(2-((E)-7-Iodo-4-methylhept-3-enyl)phenyl)pent-1-en-4-yn-3-one **117b**

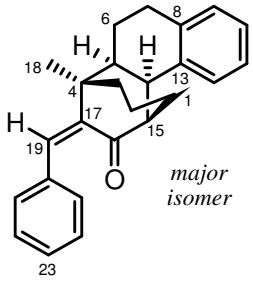


117b

Sodium iodide (250mg, 1.67mmol) was added in one portion to a stirred solution of the chloride **136b** (116mg, 0.39mmol) and potassium carbonate (2mg, 0.01mmol) in 2-butanone (8ml) at room temperature, under a nitrogen atmosphere. The solution was heated under reflux for 32h, cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O, 90% petrol) on silica gel, to leave the iodide **117b** (134mg, 89%) as a yellow oil; (Found C, 58.3; H, 5.3%. $C_{19}H_{21}IO$ requires C, 58.2; H, 5.4%); ν_{max}(sol $CHCl_3$)/cm^{-1}, 3297 (m), 2102 (m), 1635 (s), 1598 (w); δ_H (400MHz, $CDCl_3$), 1.40 (3H, app s, C*H*=CCH_3, *H*-16), 1.74-1.83 (2H, m, CH_2CH_2I, *H*-18), 2.00 (2H, t, *J* 7.5Hz, CH_2CH_2CH_2I, *H*-17), 2.23 (2H, dt, *J* 7.5 and 7.0Hz, ArCH_2CH_2, *H*-13), 2.79 (2H, t, *J* 7.0Hz, ArCH_2, *H*-12), 3.02 (2H, t, *J* 7.0Hz, CH_2I, *H*-19), 3.26 (1H, s, ≡C-*H*, *H*-1), 5.15 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH_3, *H*-14), 6.68 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 7.15-7.21 (2H, m, 2 x Ar*H*, *H*-8,10), 7.29 (1H, ddd, *J* 7.5, 7.0, 1.0Hz, Ar*H*, *H*-9), 7.53 (1H, dd, *J* 7.5 and 1.0Hz, Ar*H*, *H*-7), 8.18 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 6.6 (t, *C*-19), 15.8 (q, *C*-16), 30.2, (t, *C*-13), 31.4 (t, *C*-18), 33.4 (t, *C*-12), 40.0 (t, *C*-17), 79.2 (d, *C*-1), 80.1 (s, *C*-2), 124.1 (d, *C*-14), 126.7, 126.8 (2 x d, *C*-7,8), 128.8 (d, *C*-4), 130.5 (d, *C*-10), 131.2 (d, *C*-9),

132.2 (s, *C*-6), 134.6 (s, *C*-11), 142.6 (s, *C*-15), 147.2 (d, *C*-5), 177.7 (s, *C*-3); m/z (ES) 415.0563 ($M + Na^+$, $C_{19}H_{21}{}^{127}IONa$ requires 415.0537).

(±)-Benzylidene substituted bridged tricycle **148a**

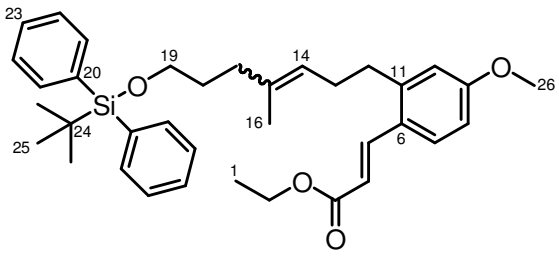


148a

A solution of tri-*n*-butyltin hydride (107µl, 0.40mmol) and 2,2'-azobis(isobutyronitrile) (32mg, 0.19mmol) in degassed benzene (13ml), was added dropwise, over 8h, *via* syringe pump to a stirred solution of the iodide **117b** (130mg, 0.33mmol) and 2,2'-azobis(isobutyronitrile) (16mg, 0.1mmol) in degassed benzene (130ml), at 80°C under an argon atmosphere. The mixture was heated under reflux for 12h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, (5–10% Et_2O, 95-90% petrol) to give the bridged tricyclic ketone **148a** (38mg, 35%) as a colorless oil (inseparable mixture of diastereoisomers in a 2:1 ratio); ν_{max}(sol $CHCl_3$)/cm^{-1}, 1694 (s), 1614 (m); δ_H (400MHz, $CDCl_3$), (major diastereoisomer) 1.40 (3H, s, CH_3, *H*-18), 1.48–1.89 (6H, m), 1.98–2.24 (3H, m)(*H*-1,2,3,5,6), 2.68 (1H, app td, *J* 15.5 and 2.5Hz, ArCH_aH$_b$, *H*-7$_a$), 2.94 (1H, app dt, *J* 15.5 and 3.5Hz, ArCH$_a$$H_b$, *H*-7$_b$), 3.28 (1H, app dt, *J* 8.0 and 3.0Hz, O=CC*H*, *H*-15), 3.38 (1H, dd, *J* 10.0 and 3.0Hz, ArC*H*, *H*-14), 6.89 (1H, s, PhC*H*, *H*-19), 7.08–7.43 (9H, m, 9 x Ar*H*, *H*-9,10,11,12,21,22,23); (minor diastereoisomer) 1.27 (3H, s, CH_3, *H*-18), 1.48–1.89 (6H, m), 1.98–2.24 (3H, m)(*H*-1,2,3,5,6), 2.86 (1H, app d, *J* 10.5 and 1.5Hz, O=CC*H*, *H*-15), 3.02 (2H, m, $ArCH_2$, *H*-7), 3.34 (1H, dd, *J* 10.5 and 1.5Hz,

ArC*H*, *H*-14), 6.71 (1H, s, PhC*H*, *H*-19), 7.08–7.43 (9H, m, 9 x Ar*H*, *H*-9,10,11,12,21,22,23); δ_C (100MHz, $CDCl_3$) (major diastereoisomer) 21.4 (t, *C*-2), 24.7 (t, *C*-6), 25.0 (t, *C*-1), 27.6 (q, *C*-18), 30.9 (t, *C*-7), 36.8 (d, *C*-14), 37.1 (t, *C*-3), 43.5 (s, *C*-4), 45.7 (d, *C*-5), 52.4 (d, *C*-15), 125.7, 126.4 (2 x d, *C*-10,11), 127.5 (d, *C*-9), 127.9 (2C d, *C*-21), 128.0 (d, *C*-23), 129.0 (2C d, *C*-22), 129.1 (d, *C*-12), 135.4 (d, *C*-19), 136.8 (s, *C*-20), 137.0 (s, *C*-8), 139.6 (s, *C*-13), 144.1 (s, *C*-17), 205.7 (s, *C*-16); (minor diastereoisomer) 21.8 (t, *C*-2), 24.0 (t, *C*-6), 24.3 (q, *C*-18), 25.8 (t, *C*-1), 28.7 (t, *C*-7), 40.7 (s, *C*-4), 43.6 (d, *C*-14), 46.0 (t, *C*-3), 46.5 (d, *C*-5), 47.2 (d, *C*-15), 123.3, 125.4 (2 x d, *C*-10,11), 126.2 (d, *C*-9), 127.8 (2C d, *C*-21), 128.6 (2C d, *C*-22), 128.9 (d, *C*-23), 129.1 (d, *C*-12), 135.1 (d, *C*-19), 136.6 (s, *C*-20), 137.4 (s, *C*-8), 139.5 (s, *C*-13), 142.6 (s, *C*-17), 206.1 (s, *C*-16); m/z (ES) 343.2053 ($M + H^+$, $C_{25}H_{27}O$ requires 343.2056).

(2E)-Ethyl 3-(2-(7-(tert-Butyl-diphenyl-silanyloxy)-4-methylhept-3-enyl)-4-methoxyphenyl)acrylate **120b**

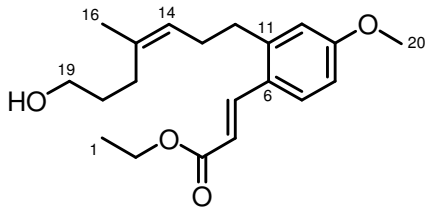


120b

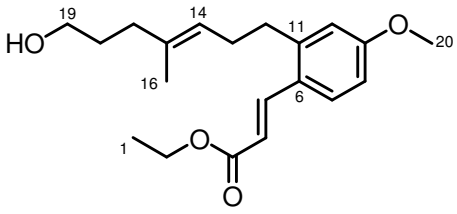
Sodium hexamethyldisilazane (2.0M in THF, 9.0ml, 18mmol) was added dropwise over 10 min, to a stirred solution of the sulfone **122** (8.25g, 16mmol) and the aldehyde **121** (3.75g, 14mmol)[71] in tetrahydrofuran (50ml) at -78°C, under a nitrogen atmosphere. The yellow mixture was stirred at -78°C for 3h and then allowed to warm to room temperature over 12h. Saturated aqueous ammonium chloride (30ml) was added, and the separated aqueous phase was

then extracted with diethyl ether (3 x 50ml). The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash colomn chromatography (5% EtOAc, 95% petrol) on silica gel, to give a 2:3 mixture of *Z* and *E* isomers of the alkene **120b** (3.30g, 55%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1706 (s), 1631 (s); δ_H (400MHz, $CDCl_3$), 1.02, 1.07 (9H, 2 x s, $SiC(CH_3)_3$, *H*-25), 1.31 (3H, 2 x t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.48-1.69 (5H, m, $CH{=}CCH_3$ + $CH_2CH_2OTBDPS$, *H*-16,18), 2.02 (2H, 2 x t, *J* 6.0Hz, $CH_2CH_2CH_2OTBDPS$, *H*-17), 2.17-2.29 (2H, m, $ArCH_2CH_2$, *H*-13), 2.72 (2H, 2 x t, *J* 7.0Hz, $ArCH_2$, *H*-12), 3.61 (2H, 2 x t, J 6.5Hz, $CH_2OTBDPS$, *H*-19), 3.81 (3H, 2 x s, OCH_3, *H*-26), 4.24 (2H, 2 x q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.16 (1H, 2 x tq, *J* 7.0 and 1.0Hz, $CH{=}CCH_3$, *H*-14), 6.26 (1H, 2 x d, *J* 16.0Hz, ArCH=CH, *H*-4), 6.73-6.78 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.32-7.45 (6H, m, 6 x Ar*H*, *H*-22,23), 7.53 (1H, 2 x d, *J* 8.5Hz, Ar*H*, *H*-7), 7.62-7.84 (4H, m, 4 x Ar*H*, *H*-21), 7.95 (1H, 2 x d, *J* 16.0Hz, ArCH=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 14.4 (q, *C*-1), 16.0 (t, *C*-18), 19.2, 19.3 (2 x s, *C*-24), 23.4 (q, *C*-16), 26.8, 26.9 (2 x q, *C*-25), 28.1 (t, *C*-17), 29.7, 30.0 (2 x t, *C*-13), 31.0 (q, *C*-16), 33.7 (2 x t, *C*-12), 35.8 (t, *C*-17), 55.3, 55.4 (2 x q, *C*-26), 60.3, 60.4 (2 x t, *C*-2), 63.7, 63.8 (2 x t, *C*-19), 112.2, 112.3 (2 x d, *C*-8), 115.1, 115.2 (2 x d, *C*-10), 116.7, 116.8 (2 x d, *C*-4), 122.9, 123.9 (2 x d, *C*-14), 125.5, 125.6 (2 x s, *C*-6), 127.6, 127.7 (2 x 2C d, *C*-22), 128.0, 128.1 (2 x d, *C*-7), 129.5, 1297 (2 x d, *C*-23), 134.1, 134.2 (2 x s, *C*-20), 135.6, 135.7 (2 x 2C d, *C*-21), 136.2, 136.3 (2 x s, *C*-15), 141.7, 141.8 (2 x d, *C*-5), 144.0, 144.1 (2 x s, *C*-11), 161.0, 161.1 (2 x s, *C*-9), 167.4, 167.5 (2 x s, *C*-3).

***(2E)-Ethyl 3-(2-((Z)-7-hydroxy-4-methylhept-3-enyl)-4-methoxyphenyl)acrylate* 131c *and (2E)-ethyl 3-(2-((E)-7-hydroxy-4-methylhept-3-enyl)-4-methoxyphenyl)acrylate* 131d**



131c

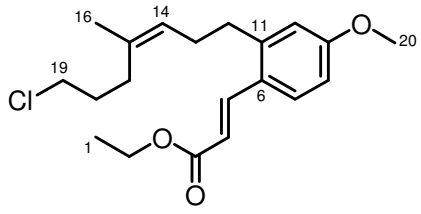


131d

A solution of tetra-*n*-butylammonium fluoride (90mg, 0.30mmol) in tetrahydrofuran (1.5ml) was added dropwise over 10 min, to a stirred solution of the silyl ether **120b** (130mg, 0.20mmol) in tetrahydrofuran (2ml) at 0^{o}C, under a nitrogen atmosphere. The pink solution was allowed to warm to room temperature over 3h and then diethyl ether (5ml) and water (5ml) were added at 0^{o}C. The separated aqueous phase was extracted with diethyl ether (3 x 25ml) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (35% Et_2O, 65% petrol) on silica gel, to give i) the *Z*-isomer of the alcohol **131c** (24mg, 32%)(eluted first) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3623 (w), 3513 (br w), 1699 (s), 1629 (s); δ_H (400MHz, $CDCl_3$), 1.33 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.62 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2OH, *H*-18), 1.70 (3H, s, $CH{=}CCH_3$, *H*-16), 2.08 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2OH$, *H*-17), 2.25 (2H, dt, *J* 8.0 and 7.0Hz, $ArCH_2CH_2$, *H*-13), 2.74 (2H, t, *J* 8.0Hz, $ArCH_2$, *H*-12), 3.59 (2H, t, *J* 6.5Hz, CH_2OH, *H*-19), 3.82 (3H, s, OCH_3, *H*-20), 4.25 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.23 (1H, t, *J* 7.0Hz, $CH{=}CCH_3$, *H*-14), 6.28 (1H, d, *J* 16.0Hz, ArCH=CH, *H*-4), 6.72 (1H, d, *J* 2.5Hz, CH_3OCCHC, *H*-10), 6.76 (1H, dd, *J* 8.5 and 2.5Hz, $CH_3OCCHCH$, *H*-8), 7.55 (1H, d, *J* 8.5Hz, $CH_3OCCHCH$, *H*-7), 8.00 (1H, d, *J* 16.0Hz, ArCH=CH, *H*-5); nOe enhancement between H-13 and

H-17 of 3%; δ_C (100MHz, $CDCl_3$), 14.3 (q, *C*-1), 23.3 (q, *C*-16), 27.9 (t, *C*-17), 30.4 (t, *C*-13), 31.0 (t, *C*-18), 34.2 (t, *C*-12), 55.3 (q, *C*-20), 60.5 (t, *C*-2), 62.5 (t, *C*-19), 112.3 (d, *C*-8), 115.2 (d, *C*-10), 116.4 (d, *C*-4), 124.2 (d, *C*-14), 125.4 (s, *C*-6), 127.9 (d, *C*-7), 136.0 (s, *C*-15), 142.0 (d, *C*-5), 144.2 (s, *C*-11), 161.1 (s, *C*-9); m/z (ES) 355.1880 ($M + Na^+$, $C_{20}H_{28}O_4Na$ requires 355.1880); and ii) the *E*-isomer of the alcohol **131d** (28mg, 37%)(eluted second) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3621 (br w), 1700 (s), 1630 (m); δ_H (400MHz, $CDCl_3$), 1.33 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.53 (3H, s, $CH{=}CCH_3$, *H*-16), 1.64 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2OH, *H*-18), 2.03 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2OH$, *H*-17), 2.26 (2H, dt, *J* 7.5 and 7.0Hz, $ArCH_2CH_2$, *H*-13), 2.76 (2H, t, *J* 7.5Hz, $ArCH_2$, *H*-12), 3.59 (2H, t, *J* 6.5Hz, CH_2OH, *H*-19), 3.82 (3H, s, OCH_3, *H*-20), 4.25 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.21 (1H, t, *J* 7.0Hz, $CH{=}CCH_3$, *H*-14), 6.27 (1H, d, *J* 16.0Hz, ArCH=CH, *H*-4), 6.71 (1H, d, *J* 2.5Hz, CH_3OCCHC, *H*-10), 6.76 (1H, dd, *J* 9.0 and 2.5Hz, $CH_3OCCHCH$, *H*-8), 7.54 (1H, d, *J* 9.0Hz, $CH_3OCCHCH$, *H*-7), 7.95 (1H, d, *J* 16.0Hz, $ArCH{=}CH$, *H*-5); nOe enhancement between H-13 and H-16 of 2%; δ_C (100MHz, $CDCl_3$), 14.3 (q, *C*-1), 15.8 (q, *C*-16), 29.8 (t, *C*-13), 30.6 (t, *C*-18), 33.5 (t, *C*-12), 35.8 (t, *C*-17), 55.2 (q, *C*-20), 60.3 (t, *C*-2), 62.6 (t, *C*-19), 112.1 (d, *C*-8), 115.2 (d, *C*-10), 116.7 (d, *C*-4), 123.2 (d, *C*-14), 125.6 (s, *C*-6), 128.0 (d, *C*-7), 136.0 (s, *C*-15), 141.7 (d, *C*-5), 143.9 (s, *C*-11), 160.9 (s, *C*-9), 167.4 (s, *C*-3); m/z (ES) 355.1880 ($M + Na^+$, $C_{20}H_{28}O_4Na$ requires 355.1880).

***(2E)-Ethyl 3-(2-((Z)-7-chloro-4-methylhept-3-enyl)-4-methoxyphenyl)acrylate* 132c**

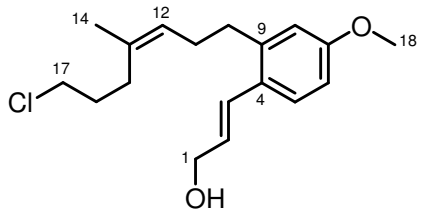


132c

N-Chlorosuccinimide (0.80g, 6.0mmol) was added in one portion, to a stirred solution of the *Z*-alcohol **131c** (1.40g, 4.3mmol), triphenylphosphine (1.45g, 5.6mmol) and potassium carbonate (0.12g, 0.9mmol) in dichloromethane (50ml) at 0°C, under a nitrogen atmosphere. The solution was stirred at 0°C for 4h and then concentrated *in vacuo*. The residue was purified by flash column chromatography (15% Et_2O, 85% petrol) on silica gel, to give the chloride **132c** (1.34g, 90%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1703 (s), 1630 (s); δ_H (400MHz, $CDCl_3$), 1.33 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.66 (3H, d, *J* 1.0Hz, $CH{=}CCH_3$, *H*-16), 1.73 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2Cl, *H*-18), 2.08 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2Cl$, *H*-17), 2.27 (2H, dt, *J* 7.5 and 7.0Hz, $ArCH_2CH_2$, *H*-13), 2.76 (2H, t, *J* 7.5Hz, $ArCH_2$, *H*-12), 3.43 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-19), 3.82 (3H, s, OCH_3, *H*-20), 4.26 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.24 (1H, app t, *J* 7.0Hz, $CH{=}CCH_3$, *H*-14), 6.27 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 6.73 (1H, d, *J* 2.5Hz, CH_3OCCHC, *H*-10), 6.77 (1H, dd, *J* 8.5 and 2.5Hz, $CH_3OCCHCH$, *H*-8), 7.54 (1H, d, *J* 8.5Hz, $CH_3OCCHCH$, *H*-7), 7.95 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 14.4 (q, *C*-1), 23.2 (q, *C*-16), 28.8 (t, *C*-17), 29.9 (t, *C*-13), 30.7 (t, *C*-18), 33.7 (t, *C*-12), 44.7 (t, *C*-19), 55.3 (q, *C*-20), 60.3 (t, *C*-2), 112.3 (d, *C*-8), 115.2 (d, *C*-10), 116.8 (d, *C*-4), 125.1 (d, *C*-14), 125.9 (s, *C*-6), 128.1 (d, *C*-7), 134.7 (s, *C*-15), 141.6 (d, *C*-5), 143.8 (s, *C*-11), 161.0 (s, *C*-9), 167.4 (s, *C*-3); m/z (ES) 351.1713 ($M + H^+$, $C_{20}H_{28}{}^{35}ClO_3$ requires 351.1721).

(2E)-3-(2-((Z)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)prop-2-en-1-ol

133c



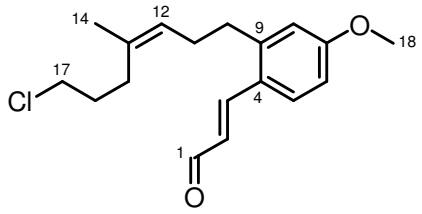
133c

Diisobutylaluminium hydride (1.0M in hexanes, 3.5ml, 3.50mmol) was added dropwise over 10 min, to a stirred solution of the ester **132c** (0.58g, 1.65mmol) in dichloromethane (30ml) at -78^{o}C under a nitrogen atmosphere. The mixture was stirred at -78^{o}C for 3h and then saturated aqueous Rochelle's salt (30ml) was added at 0^{o}C. The separated aqueous phase was extracted with dichloromethane (3 x 50ml) and the combined organic extracts were dried and then concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to give the alcohol **133c** (0.47g, 92%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3610 (br m), 1607 (s); δ_H (400MHz, $CDCl_3$), 1.68 (3H, s, CH=CCH_3, *H*-14), 1.76 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2Cl, *H*-16), 2.11 (2H, t, *J* 7.5Hz, CH_2CH_2CH_2Cl, *H*-15), 2.26 (2H, dt, *J* 8.0 and 7.0Hz, ArCH_2CH_2, *H*-11), 2.67 (2H, t, *J* 8.0Hz, ArCH_2, *H*-10), 3.45 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-17), 3.80 (3H, s, OCH_3, *H*-18), 4.32 (2H, dd, *J* 6.0 and 1.5Hz, CH_2OH, *H*-1), 5.25 (1H, app t, *J* 7.0Hz, C*H*=CCH$_3$, *H*-12), 6.17 (1H, dt, *J* 15.5 and 6.0Hz, ArCH=C*H*, *H*-2), 6.69 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-8), 6.74 (1H, dd, *J* 8.0 and 2.5Hz, CH_3OCC*H*CH, *H*-6), 6.80 (1H, app d, *J* 15.5Hz, ArC*H*=CH, *H*-3), 7.41 (1H, d, *J* 8.0Hz, CH_3OCCHC*H*, *H*-5); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-14), 28.8 (t, *C*-11), 29.3 (t, *C*-16), 30.7 (t, *C*-10), 33.8 (t, *C*-15), 44.8 (t, *C*-17), 55.2 (q, *C*-18), 64.1 (t, *C*-1), 111.8 (d, *C*-6), 114.9 (d, *C*-8), 125.5 (d, *C*-12), 127.2 (d, *C*-2), 128.0 (s, *C*-4), 128.1

(d, *C*-5), 128.4 (d, *C*-3), 134.3 (s, *C*-13), 141.1 (s, *C*-9), 159.1 (s, *C*-7); m/z (ES) 291.1507 (M^+ - OH, $C_{18}H_{24}{}^{35}ClO$ requires 291.1510).

(2E)-3-(2-((Z)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)acrylaldehyde

134c

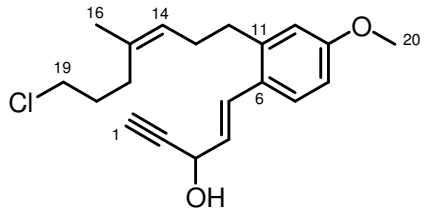


134c

Activated manganese (IV) oxide (5.80g, 66.70mmol) was added portionwise over 5 mins, to a stirred solution of the alcohol **133c** (1.03g, 3.34mmol) in dichloromethane (50ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 20h and then filtered through celite with ethyl acetate (200ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% Et_2O, 60% petrol) on silica gel, to leave the *Z*-aldehyde **134c** (0.83g, 81%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1671 (s), 1598 (s); δ_H (400MHz, $CDCl_3$), 1.67 (3H, s, CH=CCH_3, *H*-14), 1.74 (2H, tt, *J* 7.5 and 6.5Hz, C$H_2$$CH_2$Cl, *H*-16), 2.09 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2Cl$, *H*-15), 2.31 (2H, dt, *J* 7.5 and 7.0Hz, ArCH_2CH_2, *H*-11), 2.80 (2H, t, *J* 7.0Hz, ArCH_2, *H*-10), 3.43 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-17), 3.85 (3H, s, OCH_3, *H*-18), 5.24 (1H, app t, *J* 7.5Hz, C*H*=CCH_3, *H*-12), 6.60 (1H, dd, *J* 16.0 and 8.0Hz, ArCH=C*H*, *H*-2), 6.77 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-8), 6.81 (1H, dd, *J* 8.0 and 2.5Hz, CH_3OCC*H*CH, *H*-6), 7.60 (1H, d, *J* 8.0Hz, CH_3OCCHC*H*, *H*-5), 7.73 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-3), 9.68 (1H, d, *J* 8.0Hz, C(O)*H*, *H*-1); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-14), 28.7 (t, *C*-15), 29.9 (t, *C*-11), 30.5 (t, *C*-16), 33.6 (t, *C*-10), 44.6 (t, *C*-17), 55.4 (q, *C*-18), 112.6 (d, *C*-6), 115.5 (d, *C*-8), 124.8 (d, *C*-12), 124.9 (s, *C*-4),

127.4 (d, *C*-2), 128.7 (d, *C*-5), 135.0 (s, *C*-13), 144.4 (s, *C*-9), 149.8 (d, *C*-3), 161.9 (s, *C*-7), 193.8 (s, *C*-1); m/z (ES) 329.1280 (M + Na^+, $C_{18}H_{23}{}^{35}ClO_2Na$ requires 329.1279).

***(±)-(1E)-1-(2-((Z)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)pent-1-en-4-yn-3-ol* 135c**

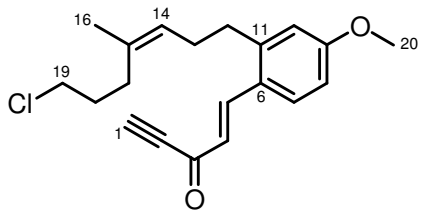


135c

Ethynylmagnesium bromide (0.5M in THF, 7.8ml, 3.9mmol) was added dropwise over 5 min, to a stirred solution of the aldehyde **134c** (0.80g, 2.6mmol) in tetrahydrofuran (45ml) at -78°C, under a nitrogen atmosphere. The mixture was allowed to warm to room temperature over 20h, and then diethyl ether (30ml) and saturated aqueous ammonium chloride (50ml) were added at room temperature. The separated aqueous phase was extracted with diethyl ether (3 x 80ml) and the combined organic extracts were then washed with brine (20ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to give the alkyne **135c** (0.86g, 99%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3593 (br m), 3305 (s), 1606 (s); δ_H (400MHz, $CDCl_3$), 1.68 (3H, d, *J* 1.0Hz, CH=CCH_3, *H*-16), 1.75 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2Cl, *H*-18), 2.00 (1H, d, *J* 6.5Hz, O*H*), 2.10 (2H, t, *J* 7.5Hz, C$H_2CH_2CH_2Cl$, *H*-17), 2.27 (2H, dt, *J* 8.0 and 7.5Hz, $ArCH_2CH_2$, *H*-13), 2.64 (1H, d, *J* 2.0Hz, ≡C-*H*, *H*-1), 2.68 (2H, t, *J* 8.0Hz, ArCH_2, *H*-12), 3.45 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-19), 3.80 (3H, s, OCH_3, *H*-20), 5.04-5.09 (1H, m, HOC*H*, *H*-3), 5.25 (1H, app t, *J* 7.5Hz, C*H*=CCH_3, *H*-14), 6.11 (1H, dd, *J* 15.5 and 6.0Hz, ArCH=C*H*, *H*-4), 6.70

(1H, d, *J* 2.5Hz, CH_3OCCHC, *H*-10), 6.74 (1H, dd, *J* 8.5 and 2.5Hz, $CH_3OCCHCH$, *H*-8), 7.02 (1H, d, *J* 15.5Hz, ArC*H*=CH, *H*-5), 7.42 (1H, d, *J* 8.5Hz, $CH_3OCCHCH$, *H*-7); δ_C (100MHz, $CDCl_3$), 23.2 (q, *C*-16), 29.4 (t, *C*-13), 30.7 (t, *C*-18), 33.8 (t, *C*-12), 35.2 (t, *C*-17), 44.8 (t, *C*-19), 55.2 (q, *C*-20), 63.1 (d, *C*-3), 77.2 (d, *C*-1), 83.0 (s, *C*-2), 108.1 (d, *C*-8), 115.0 (d, *C*-10), 124.6 (d, *C*-14), 126.9 (d, *C*-7), 127.2 (s, *C*-6), 127.4 (d, *C*-4), 129.6 (d, *C*-5), 134.4 (s, *C*-15), 145.0 (s, *C*-11), 159.5 (s, *C*-9); m/z (ES) 355.1434 ($M + Na^+$, $C_{20}H_{25}{}^{35}ClO_2Na$ requires 355.1441).

(1E)-1-(2-((Z)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)pent-1-en-4-yn-3-one **136c**

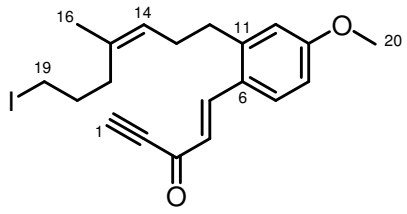


136c

Activated manganese (IV) oxide (4.34g, 49.9mmol) was added portionwise over 5 mins, to a stirred solution of the *Z*-alcohol **135c** (0.83g, 2.5mmol) in dichloromethane (45ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 23h, then filtered through celite with dichloromethane (50ml) and warm ethyl acetate, (100ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to give the ketone **136c** (0.77g, 86%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3297 (m), 2101 (m), 1630 (s), 1596 (s); δ_H (400MHz, $CDCl_3$), 1.66 (3H, d, *J* 1.0Hz, CH=CCH_3, *H*-16), 1.72 (2H, tt, *J* 7.5 and 6.5Hz, C$H_2$$CH_2Cl$, *H*-18), 2.06 (2H, t, *J* 7.5Hz, C$H_2$$CH_2CH_2Cl$, *H*-17), 2.32 (2H, dt, *J* 7.5 and 7.0Hz, $ArCH_2$CH_2, *H*-13), 2.81 (2H, t, *J* 7.0Hz, ArCH_2, *H*-12), 3.30 (1H, s,

≡C-H, *H*-1), 3.42 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-19), 3.85 (3H, s, OCH_3, *H*-20), 5.24 (1H, app t, *J* 7.5Hz, C*H*=CCH$_3$, *H*-14), 6.67 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 6.77 (1H, d, *J* 2.5Hz, CH$_3$OCC*H*C, *H*-10), 6.80 (1H, dd, *J* 8.5 and 2.5Hz, CH$_3$OCC*H*CH, *H*-8), 7.60 (1H, d, *J* 8.5Hz, CH$_3$OCCHC*H*, *H*-7), 8.20 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, CDCl$_3$), 23.3 (q, *C*-16), 28.8, 30.1, 30.7, 33.8 (4 x t, *C*-12,13,17,18), 44.7 (t, *C*-19), 55.4 (q, *C*-20), 78.7 (d, *C*-1), 80.3 (s, *C*-2), 112.7, 115.6 (2 x d, *C*-8,10), 124.7 (d, *C*-14), 124.9 (s, *C*-6), 126.4 (d, *C*-7), 128.6 (d, *C*-4), 135.0 (s, *C*-15), 145.1 (s, *C*-11), 147.0 (d, *C*-5), 162.1 (s, *C*-9), 177.6 (s, *C*-3); m/z (ES) 331.1433 (M + H$^+$, $C_{20}H_{24}{}^{35}ClO_2$ requires 331.1459).

(1E)-1-(2-((Z)-7-Iodo-4-methylhept-3-enyl)-4-methoxyphenyl)pent-1-en-4-yn-3-one **117c**

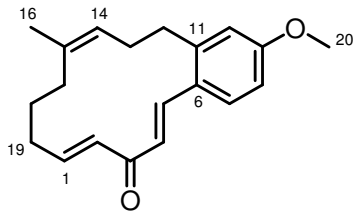


117c

Sodium iodide (270mg, 1.81mmol) was added in one portion, to a stirred solution of the Z- chloride **136c** (115mg, 0.34mmol) and potassium carbonate (3mg, 0.02mmol) in 2-butanone (6ml) at room temperature under a nitrogen atmosphere. The mixture was heated under reflux for 23h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O, 90% petrol) on silica gel, to give the iodide **117c** (135mg, 92%) as a yellow solid; m.p = 80-81^{o}C (petrol); ν_{max}(sol CHCl$_3$)/cm^{-1}, 3297 (m), 2101 (w), 1631 (s), 1596 (s); δ_H (400MHz, CDCl$_3$), 1.65 (3H, d, J 1.0Hz, CH=CCH_3, *H*-16), 1.76 (2H, tt, *J* 7.5 and 7.0Hz, CH_2CH$_2$I, *H*-18), 2.00 (2H, t, *J* 7.5Hz, CH_2CH$_2$CH$_2$I, *H*-17), 2.34 (2H, dt, *J* 7.5 and 7.0Hz, ArCH$_2$CH_2, *H*-13), 2.82 (2H, t, *J* 7.0Hz,

ArCH_2, *H*-12), 3.05 (2H, t, *J* 7.0Hz, CH_2I, *H*-19), 3.30 (1H, s, ≡C-*H*, *H*-1), 3.85 (3H, s, OCH_3, *H*-20), 5.23 (1H, app t, *J* 7.5Hz, C*H*=CCH_3, *H*-14), 6.68 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 6.78 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-10), 6.81 (1H, dd, *J* 8.5 and 2.5Hz, CH_3OCC*H*CH, *H*-8), 7.60 (1H, d, *J* 8.5Hz, CH_3OCCHC*H*, *H*-7), 8.20 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 6.5 (t, *C*-19), 23.2 (q, *C*-16), 30.2, (t, *C*-13), 31.7 (t, *C*-18), 32.4 (t, *C*-17), 33.7 (t, *C*-12), 55.5 (q, *C*-20), 78.8 (d, *C*-1), 80.3 (s, *C*-2), 112.7 (d, *C*-8), 115.7 (d, *C*-10), 124.8 (d, *C*-14), 124.9 (s, *C*-6), 126.4 (d, *C*-4), 128.7 (d, *C*-7), 134.9 (s, *C*-15), 145.0 (s, *C*-11), 147.0 (d, *C*-5), 162.1 (s, *C*-9), 180.1 (s, *C*-3); m/z (ES) 445.0610 (M + Na^+, $C_{20}H_{23}{}^{127}IO_2Na$ requires 445.0640).

(5*E*,8*E*)-11,12,13,14,15,16-Hexahydro-2-methoxy-13-methylbenzo[14]annulen-7(10H)-one 137b



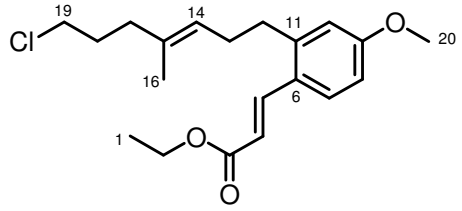
137b

A solution of tri-*n*-butyltin hydride (85µl, 0.32mmol) and 2,2'-azobis(isobutyronitrile) (26mg, 0.16mmol) in degassed benzene (11ml) was added dropwise, over 8h, *via* syringe pump to a stirred solution of the iodide **117c** (110mg, 0.26mmol) and 2,2'-azobis(isobutyronitrile) (13mg, 0.08mmol) in degassed benzene (110ml) at 80^{o}C under an argon atmosphere. The mixture was heated under reflux for a further 12h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (5–10% Et_2O, 95-90% pentane) on silica gel to leave the macrocycle **137b** (28mg, 36%) as a yellow oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1640 (s), 1602 (s); δ_H (400MHz,

$CDCl_3$), 1.63-1.80 (2H, m, CH=CHCH$_2$CH_2, *H*-18), 1.82 (3H, s, CH=CCH_3, *H*-16), 2.10-2.19 (4H, m, ArCH$_2$CH_2 + CH=CHCH$_2$CH$_2$CH_2, *H*-13,17), 2.39 (2H, dtd, *J* 7.0, 4.0 and 1.0Hz, CH=CHCH_2, *H*-19), 2.66 (2H, app t, *J* 6.0Hz, ArCH_2, *H*-12), 3.84 (3H, s, OCH_3, *H*-20), 5.38 (1H, t, *J* 7.5Hz, C*H*=CCH$_3$, *H*-14), 6.20 (1H, dt, *J* 15.5 and 1.0Hz, O=CC*H*=CH, *H*-2), 6.58 (1H, dt, *J* 15.5 and 4.0Hz, O=CCH=C*H*, *H*-1), 6.75 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 6.79 (1H, d, *J* 1.5Hz, CH$_3$OCC*H*C, *H*-10), 6.84 (1H, dd, *J* 7.0 and 1.5Hz, CH$_3$OCC*H*CH, *H*-8), 7.55 (1H, d, *J* 7.0Hz, CH$_3$OCCHC*H*, *H*-7), 7.88 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 23.0 (q, *C*-16), 29.0 (t, *C*-18), 30.1 (t, *C*-17), 31.5 (t, *C*-13), 32.1 (t, *C*-19), 35.5 (t, *C*-12), 55.4 (q, *C*-20), 123.3 (d, *C*-14), 125.7 (d, *C*-8), 127.0 (d, *C*-7), 127.7 (d, *C*-10), 130.4 (d, *C*-4), 130.3 (d, *C*-2), 130.8 (d, *C*-9), 132.3 (s, *C*-15), 137.9 (s, *C*-6), 142.1 (s, *C*-11), 142.7 (d, *C*-5), 147.6 (d, *C*-1), 198.3 (s, *C*-3); m/z (ES) 297.1864 ($M + H^+$, $C_{20}H_{25}O_2$ requires 297.1854).

(2E)-Ethyl-3-(2-((E)-7-chloro-4-methylhept-3-enyl)-4-methoxyphenyl)acrylate

132d



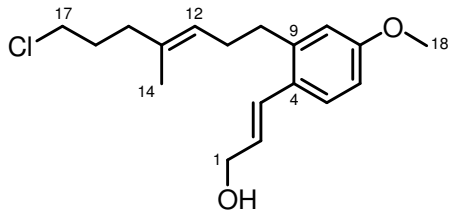
132d

N-Chlorosuccinimide (1.1g, 8.3mmol) was added in one portion, to a stirred solution of the alcohol **131d** (2.0g, 5.9mmol), triphenylphosphine (2.0g, 7.7mmol) and potassium carbonate (0.16g, 1.2mmol) in dichloromethane (50ml) at 0^{o}C, under a nitrogen atmosphere. The solution was stirred at 0^{o}C for 4h and then concentrated *in vacuo*. The residue was purified by flash column chromatography (15% Et_2O, 85% petrol) on silica gel, to leave the chloride **132d** (1.9g, 91%) as a

colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1698 (s), 1631 (s); δ_H (400MHz, $CDCl_3$), 1.33 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-1), 1.52 (3H, d, *J* 1.0Hz, $CH{=}CCH_3$, *H*-16), 1.83 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2Cl, *H*-18), 2.09 (2H, t, *J* 7.5Hz, $CH_2CH_2CH_2Cl$, *H*-17), 2.27 (2H, dt, *J* 8.0 and 7.5Hz, $ArCH_2CH_2$, *H*-13), 2.76 (2H, t, *J* 8.0Hz, $ArCH_2$, *H*-12), 3.46 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-19), 3.82 (3H, s, OCH_3, *H*-20), 4.26 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-2), 5.21 (1H, tq, *J* 7.5 and 1.0Hz, $CH{=}CCH_3$, *H*-14), 6.27 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 6.72 (1H, d, *J* 2.5Hz, CH_3OCCHC, *H*-10), 6.77 (1H, dd, *J* 8.5 and 2.5Hz, $CH_3OCCHCH$, *H*-8), 7.55 (1H, d, *J* 8.5Hz, $CH_3OCCHCH$, *H*-7), 7.96 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 14.4 (q, *C*-1), 15.8 (q, *C*-16), 29.9 (t, *C*-13), 30.7 (t, *C*-18), 33.5 (t, *C*-12), 36.6 (t, *C*-17), 44.6 (t, *C*-19), 55.3 (q, *C*-20), 60.3 (t, *C*-2), 112.2 (d, *C*-8), 115.3 (d, *C*-10), 116.8 (d, *C*-4), 124.1 (d, *C*-14), 125.6 (s, *C*-6), 128.0 (d, *C*-7), 134.7 (s, *C*-15), 144.6 (d, *C*-5), 143.8 (s, *C*-11), 161.0 (s, *C*-9), 167.4 (s, *C*-3); m/z (ES) 351.1720 ($M + H^+$, $C_{20}H_{28}{}^{35}ClO_3$ requires 351.1721).

(2E)-3-(2-((E)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)prop-2-en-1-ol

133d



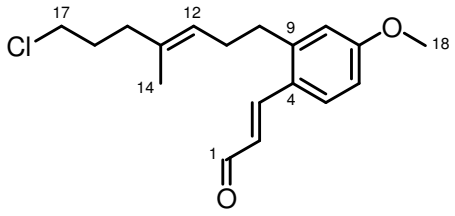
133d

Diisobutylaluminium hydride (1.0M in hexanes, 4.50ml, 4.50mmol) was added dropwise over 10 min, to a stirred solution of the ester **132d** (0.75g, 2.14mmol) in dichloromethane (30ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 3h and then a saturated aqueous solution of Rochelle's salt

(30ml) was added at 0°C. The aqueous phase was extracted with dichloromethane (3 x 50ml) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to leave the alcohol **133d** (0.58g, 87%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3610 (br m), 1607 (s); δ_H (400MHz, $CDCl_3$), 1.53 (3H, app s, CH=CCH_3, *H*-14), 1.84 (2H, tt, *J* 7.5 and 6.5Hz, CH_2CH_2Cl, *H*-16), 2.11 (2H, t, *J* 7.5Hz, CH_2CH_2CH_2Cl, *H*-15), 2.26 (2H, dt, *J* 8.0 and 7.5Hz, ArCH_2CH_2, *H*-11), 2.67 (2H, t, *J* 8.0Hz, ArCH_2, *H*-10), 3.47 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-17), 3.80 (3H, s, OCH_3, *H*-18), 4.33 (2H, dd, *J* 6.0 and 1.5Hz, CH_2OH, *H*-1), 5.23 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH_3, *H*-12), 6.17 (1H, dt, *J* 15.5 and 6.0Hz, ArCH=C*H*, *H*-2), 6.68 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-8), 6.74 (1H, dd, *J* 8.5 and 2.5Hz, CH_3OCC*H*CH, *H*-6), 6.81 (1H, app d, *J* 15.5Hz, ArC*H*=CH, *H*-3), 7.41 (1H, d, *J* 8.5Hz, CH_3OCCHC*H*, *H*-5); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-14), 29.3 (t, *C*-11), 30.7 (t, *C*-16), 33.5 (t, *C*-10), 36.7 (t, *C*-15), 44.6 (t, *C*-17), 55.2 (q, *C*-18), 64.2 (t, *C*-1), 111.7 (d, *C*-6), 114.9 (d, *C*-8), 124.6 (d, *C*-12), 127.2 (d, *C*-2), 128.0 (d, *C*-5), 128.1 (s, *C*-4), 128.6 (d, *C*-3), 134.3 (s, *C*-13), 141.1 (s, *C*-9), 159.1 (s, *C*-7); m/z (ES) 331.1422 (M + Na^+, $C_{18}H_{25}{}^{35}ClO_2Na$ requires 331.1441).

(2E)-3-(2-((E)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)acrylaldehyde

134d

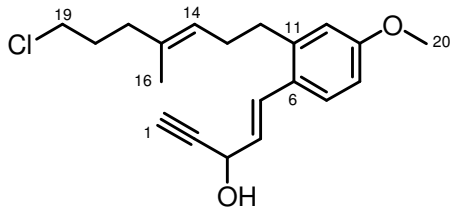


134d

Activated manganese (IV) oxide (0.56g, 6.4mmol) was added portionwise, to a stirred solution of the alcohol **133d** (0.10g, 0.3mmol) in dichloromethane (15ml) at

room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 24h, filtered through celite with dichloromethane (100ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to leave the aldehyde **134d** (0.08g, 81%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1671 (s), 1595 (s); δ_H (400MHz, $CDCl_3$), 1.51 (3H, app s, CH=CCH_3, *H*-14), 1.83 (2H, tt, *J* 7.5 and 6.5Hz, C$H_2$$CH_2$Cl, *H*-16), 2.11 (2H, t, *J* 7.5Hz, C$H_2$$CH_2$$CH_2$Cl, *H*-15), 2.30 (2H, dt, *J* 7.5 and 7.0Hz, ArCH_2CH_2, *H*-11), 2.80 (2H, t, *J* 7.0Hz, ArCH_2, *H*-10), 3.46 (2H, t, *J* 6.5Hz, CH_2Cl, *H*-17), 3.85 (3H, s, OCH_3, *H*-18), 5.22 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH_3, *H*-12), 6.61 (1H, dd, *J* 15.5 and 7.5Hz, ArCH=C*H*, H-2), 6.76 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-8), 6.81 (1H, dd, *J* 8.5 and 2.5Hz, CH_3OCC*H*CH, *H*-6), 7.60 (1H, d, *J* 8.5Hz, CH_3OCCHC*H*, *H*-5), 7.73 (1H, d, *J* 15.5Hz, ArC*H*=CH, *H*-3), 9.68 (1H, d, *J* 7.5Hz, C(O)*H*, *H*-1); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-14), 29.9 (t, *C*-11), 30.6 (t, *C*-16), 33.4 (t, *C*-10), 36.6 (t, *C*-15), 44.5 (t, *C*-17), 55.4 (q, *C*-18), 112.4 (d, *C*-6), 115.6 (d, *C*-8), 123.9 (d, *C*-12), 125.0 (s, *C*-4), 127.4 (d, *C*-2), 128.6 (d, *C*-5), 128.7 (s, *C*-13), 144.4 (s, *C*-9), 149.8 (d, *C*-3), 161.9 (s, *C*-7), 193.8 (s, *C*-1); m/z (ES) 329.1297 ($M + Na^+$, $C_{18}H_{23}{}^{35}ClO_2Na$ requires 329.1279).

(±)-(1E)-1-(2-((E)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)pent-1-en-4-yn-3-ol **135d**

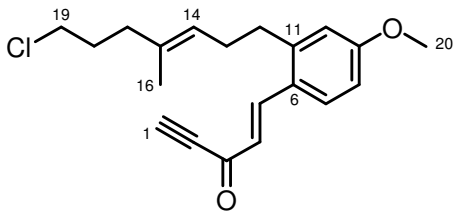


135d

Ethynylmagnesium bromide (0.5M in THF, 12.9ml, 6.50mmol) was added dropwise over 5 min, to a stirred solution of the aldehyde **134d** (1.32g, 4.30mmol)

in tetrahydrofuran (45ml) at -78°C, under a nitrogen atmosphere. The solution was slowly warmed to room temperature over 20 h and then diethyl ether (30ml) and a saturated aqueous ammonium chloride solution (50ml) were added. The aqueous phase was extracted with diethyl ether (3 x 80ml) and the combined organic extracts were washed with brine (20ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to leave the alkyne **135d** (1.33g, 93%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3591 (br m), 3305 (s), 1608 (s); δ_H (400MHz, $CDCl_3$), 1.53 (3H, app s, CH=CC*H*$_3$, *H*-16), 1.84 (2H, tt, *J* 7.5 and 7.0Hz, C*H*$_2$CH$_2$Cl, *H*-18), 2.01 (1H, d, *J* 6.5Hz, O*H*), 2.11 (2H, t, *J* 7.0Hz, C*H*$_2$CH$_2$CH$_2$Cl, *H*-17), 2.27 (2H, dt, *J* 8.0 and 7.5Hz, ArCH$_2$C*H*$_2$, *H*-13), 2.64 (1H, d, *J* 2.0Hz, ≡C-*H*, *H*-1), 2.69 (2H, t, *J* 8.0Hz, ArC*H*$_2$, *H*-12), 3.46 (2H, t, *J* 7.5Hz, C*H*$_2$Cl, *H*-19), 3.80 (3H, s, OC*H*$_3$, *H*-20), 5.03-5.09 (1H, m, C*H*OH, *H*-3), 5.22 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH$_3$, *H*-14), 6.11 (1H, dd, *J* 15.5 and 6.0Hz, ArCH=C*H*, *H*-4), 6.69 (1H, d, *J* 2.5Hz, CH$_3$OCC*H*C, *H*-10), 6.74 (1H, dd, *J* 8.5 and 2.5Hz, CH$_3$OCC*H*CH, *H*-8), 7.02 (1H, d, *J* 15.5Hz, ArC*H*=CH, *H*-5), 7.42 (1H, d, *J* 8.5Hz, CH$_3$OCCHC*H*, *H*-7); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-16), 29.4 (t, *C*-13), 30.7 (t, *C*-18), 33.5 (t, *C*-12), 36.6 (t, *C*-17), 44.6 (t, *C*-19), 55.2 (q, *C*-20), 63.1 (d, *C*-3), 74.5 (d, *C*-1), 83.0 (s, *C*-2), 111.8 (d, *C*-8), 115.0 (d, *C*-10), 124.5 (d, *C*-14), 126.9 (d, *C*-7), 127.2 (s, *C*-6), 127.4 (d, *C*-4), 129.6 (d, *C*-5), 134.3 (s, *C*-15), 141.6 (s, *C*-11), 159.5 (s, *C*-9); m/z (ES) 355.1423 (M + Na^+, $C_{20}H_{25}{}^{35}ClO_2Na$ requires 355.1441).

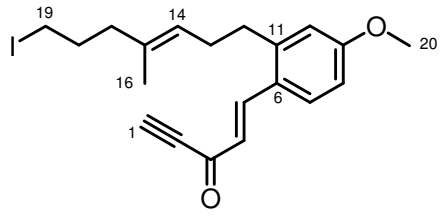
(1E)-1-(2-((E)-7-Chloro-4-methylhept-3-enyl)-4-methoxyphenyl)pent-1-en-4-yn-3-one **136d**



136d

Activated manganese (IV) oxide (0.260g, 3.00mmol) was added portionwise, to a stirred solution of the alcohol **135d** (0.050g, 0.15mmol) in dichloromethane (5ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 18h, filtered through celite with dichloromethane (50ml) and warm ethyl acetate (50ml) and then concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to leave the ketone **136d** (0.044g, 88%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3297 (m), 2101 (m), 1631 (s), 1594 (s); δ_H (400MHz, $CDCl_3$), 1.51 (3H, app s, CH=CC*H*$_3$, *H*-16), 1.83 (2H, tt, *J* 7.5 and 6.5Hz, C*H*$_2$CH$_2$Cl, *H*-18), 2.10 (2H, t, *J* 7.5Hz, C*H*$_2$CH$_2$CH$_2$Cl, *H*-17), 2.31 (2H, dt, *J* 7.5 and 7.0Hz, ArCH$_2$C*H*$_2$, *H*-13), 2.81 (2H, t, *J* 7.0Hz, ArC*H*$_2$, *H*-12), 3.20 (3H, s, ≡C-*H*, *H*-1), 3.45 (2H, t, *J* 6.5Hz, C*H*$_2$Cl, *H*-19), 3.85 (3H, s, OC*H*$_3$, *H*-20), 5.22 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH$_3$, *H*-14), 6.68 (1H, d, *J* 15.5Hz, ArCH=C*H*, *H*-4), 6.76 (1H, d, *J* 2.5Hz, CH$_3$OCC*H*C, *H*-10), 6.80 (1H, dd, *J* 8.5 and 2.5Hz, CH$_3$OCC*H*CH, *H*-8), 7.60 (1H, d, *J* 8.5Hz, CH$_3$OCCHC*H*, *H*-7), 8.21 (1H, d, *J* 15.5Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 15.8 (q, *C*-16), 30.1, 30.6, 33.6, 36.6 (4 x t, *C*-12,13,17,18), 44.4 (t, *C*-19), 55.4 (q, *C*-20), 78.7 (d, *C*-1), 80.2 (s, *C*-2), 112.5, 115.6 (2 x d, *C*-8,10), 123.9 (d, *C*-14), 124.8 (s, C-6), 126.4 (d, *C*-7), 128.6 (d, *C*-4), 134.9 (s, *C*-15), 145.1 (s, *C*-11), 146.9 (d, *C*-5), 162.1 (s, *C*-9), 177.6 (s, *C*-3); m/z (ES) 331.1456 (M + H^+, $C_{20}H_{24}{}^{35}ClO_2$ requires 331.1459).

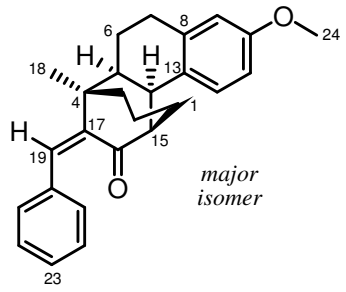
(1E)-1-(2-((E)-7-Iodo-4-methylhept-3-enyl)-4-methoxyphenyl)pent-1-en-4-yn-3-one **117d**



117d

Sodium iodide (310mg, 2.07mmol) was added in one portion, to a stirred solution of the chloride **136d** (110mg, 0.33mmol) and potassium carbonate (3mg, 0.02mmol) in 2-butanone (6ml) at room temperature, under a nitrogen atmosphere. The mixture was heated under reflux for 24h and then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O, 90% petrol) on silica gel, to leave the iodide **117d** (133mg, 95%) as a yellow oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3297 (s), 2101 (w), 1634 (s), 1592 (m); δ_H (400MHz, $CDCl_3$), 1.50 (3H, app s, CH=CCH_3, *H*-16), 1.87 (2H, tt, *J* 7.5 and 7.0Hz, CH_2CH_2I, *H*-18), 2.05 (2H, t, *J* 7.0Hz, CH_2CH_2CH_2I, *H*-17), 2.30 (2H, dt, *J* 7.5 and 7.0Hz, ArCH_2CH_2, *H*-13), 2.81 (2H, t, *J* 7.0Hz, ArCH_2, *H*-12), 3.09 (2H, t, *J* 7.5Hz, CH_2I, *H*-19), 3.30 (1H, s, ≡C-*H*, *H*-1), 3.85 (3H, s, OCH_3, *H*-20), 5.24 (1H, tq, *J* 7.5 and 1.0Hz, C*H*=CCH_3, *H*-14), 6.68 (1H, d, *J* 16.0Hz, ArCH=C*H*, *H*-4), 6.76 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-10), 6.80 (1H, dd, *J* 8.5 and 2.5Hz, CH_3OCC*H*CH, *H*-8), 7.60 (1H, d, *J* 8.5Hz, CH_3OCCHC*H*, *H*-7), 8.20 (1H, d, *J* 16.0Hz, ArC*H*=CH, *H*-5); δ_C (100MHz, $CDCl_3$), 6.5 (t, *C*-19), 15.8 (q, *C*-16), 30.1, (t, *C*-13), 31.4 (t, *C*-18), 33.5 (t, *C*-12), 40.0 (t, *C*-17), 55.4 (q, *C*-20), 78.8 (d, *C*-1), 80.2 (s, *C*-2), 112.5 (d, *C*-8), 115.6 (d, *C*-10), 124.1 (d, *C*-14), 124.8 (s, *C*-6), 126.4 (d, *C*-4), 128.6 (d, *C*-7), 134.6 (s, *C*-15), 145.0 (s, *C*-11), 146.9 (d, *C*-5), 162.1 (s, *C*-9), 177.6 (s, *C*-3); m/z (ES) 445.0629 (M + Na^+, $C_{20}H_{23}{}^{127}IO_2Na$ requires 445.0640).

***(±)-Benzylidene substituted methoxy bridged tricycle* 148b**

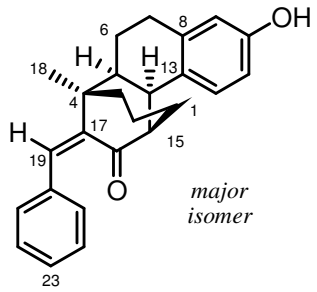


148b

A solution of tri-*n*-butyltin hydride (170µl, 0.61mmol) and 2,2'-azobis(isobutyronitrile) (25mg, 0.15mmol) in degassed benzene (20ml), was added dropwise over 8h *via* syringe pump, to a stirred solution of the iodide **117d** (200mg, 0.51mmol) and 2,2'-azobis(isobutyronitrile) (50mg, 0.30mmol) in degassed benzene (200ml), at 80^{o}C under an argon atmosphere. The mixture was heated under reflux for a further 12h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (2–10% Et_2O, 98-90% petrol) to give the bridged tricyclic ketone **148b** (45mg, 30%) as an inseparable mixture of diastereoisomers in a 2:1 ratio, as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1693 (s), 1612 (s); δ_H (400MHz, $CDCl_3$), (major diastereoisomer) 1.39 (3H, s, CH_3, *H*-18), 1.47–1.63 (3H, m), 1.69–1.85 (3H, m), 2.01–2.19 (3H, m)(*H*-1,2,3,5,6), 2.67 (1H, app td, *J* 15.5 and 3.0Hz, ArCH_aH_b, *H*-7_a), 2.89 (1H, app dt, *J* 15.5 and 3.5Hz, ArCH_aH_b, *H*-7_b), 3.21 (1H, ddd, *J* 8.0 and 3.0Hz, and 2.5Hz, O=C*CH*, *H*-15), 3.32 (1H, dd, *J* 10.0 and 3.0Hz, Ar*CH*, *H*-14), 3.80 (3H, s, OCH_3, *H*-24), 6.69 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-9), 6.77 (1H, dd, *J* 8.5 and 2.5Hz, CH_3OCC*H*CH, *H*-11), 6.87 (1H, s, PhC*H*=, *H*-19), 7.17 (1H, d, *J* 8.5Hz, CH_3OCCHC*H*, *H*-12), 7.26–7.44 (5H, m, 5 x Ph*H*, *H*-21,22,23); (minor diastereoisomer) 1.27 (3H, s, CH_3, *H*-18), 1.51–1.82 (6H, m), 1.96–2.19 (3H,m)(*H*-1,2,3,5,6), 2.81 (1H, app d, *J* 8.5Hz, O=C*CH*, *H*-15), 3.00

(2H, app t, *J* 8.5Hz, ArCH_2, *H*-7), 3.29 (1H, dd, *J* 8.5 and 1.5Hz, ArC*H*, *H*-14), 3.79 (3H, s, OCH_3, *H*-24), 6.68 (1H, d, *J* 3.0Hz, CH_3OCC*H*C, *H*-9), 6.71 (1H, s, PhC*H*=, *H*-19), 6.78 (1H, dd, *J* 8.5 and 3.0Hz, CH_3OCC*H*CH, *H*-11), 7.00 (1H, d, *J* 8.5Hz, CH_3OCCHC*H*, *H*-12), 7.26–7.38 (5H, m, 5 x Ph*H*, *H*-21,22,23); δ_C (100MHz, $CDCl_3$), (major diastereoisomer) 21.4 (t, *C*-2), 24.7 (t, *C*-6), 24.8 (t, *C*-1), 27.6 (q, *C*-18), 31.2 (t, *C*-7), 36.1 (d, *C*-14), 36.9 (t, *C*-3), 43.4 (s, *C*-4), 45.7 (d, *C*-5), 52.6 (d, *C*-15), 55.2 (q, *C*-24), 112.4 (d, *C*-11), 113.3 (d, *C*-9), 127.8 (2C d, *C*-21), 127.9 (d, *C*-23), 128.5 (d, *C*-12), 128.7 (s, *C*-13), 129.0 (2C d, *C*-22), 135.3 (d, *C*-19), 136.9 (s, *C*-20), 140.7 (s, *C*-8), 144.0 (s, *C*-17), 157.4 (s, *C*-10), 205.8 (s, *C*-16); (minor diastereoisomer) 21.8 (t, *C*-2), 23.7 (t, *C*-6), 24.2 (q, *C*-18), 25.9 (t, *C*-1), 29.1 (t, *C*-7), 40.7 (s, *C*-4), 42.9 (d, *C*-14), 46.0 (t, *C*-3), 46.7 (d, *C*-5), 47.3 (d, *C*-15), 55.2 (q, *C*-24), 110.6 (d, *C*-11), 114.4 (d, *C*-9), 124.2 (d, *C*-23), 127.7 (2C d, *C*-21), 127.8 (d, *C*-12), 129.0 (2C d, *C*-22), 131.6 (s, *C*-13), 135.0 (d, *C*-19), 136.6 (s, *C*-20), 138.7 (s, *C*-8), 142.6 (s, *C*-17), 158.0 (s, *C*-10), 206.1(s, *C*-16); m/z (ES) 373.2155 ($M + H^+$, $C_{26}H_{29}O_2$ requires 373.2162).

(±)-Phenolic bridged tricycle **147**



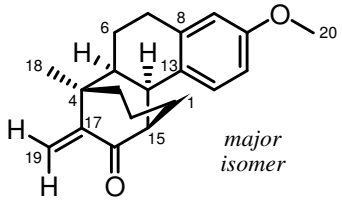
147

Boron tribromide (50µl, 0.53mmol) was added dropwise, to a stirred solution of the tricycle **148b** (50mg, 0.13mmol) in dichloromethane (10ml) at -78°C, under a nitrogen atmosphere. The solution was warmed to room temperature slowly over

13h, and then quenched with water (50ml). The separated aqueous phase was extracted with dichloromethane (3 x 50ml) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash column chromatography, (10% Et_2O, 90% petrol) to give a 2:1 mixture of diastereoisomers of the phenol **147** (23mg, 48%) as a viscous liquid solid. Crystallisation from diethyl ether and pentane gave the major diastereoisomer as colourless crystals; mp = 195–196°C; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3597 (br m), 1693 (s), 1608 (s); δ_H (400MHz, $CDCl_3$), (major diastereoisomer) 1.39 (3H, s, C*H*$_3$, *H*-18), 1.46–1.62 (3H, m), 1.69–1.85 (3H, m), 2.01–2.20 (3H, m)(*H*-1,2,3,5,6), 2.63 (1H, app td, *J* 15.5 and 3.5Hz, ArC*H*$_a$H$_b$, *H*-7$_a$), 2.85 (1H, app dt, *J* 15.5 and 3.0Hz, ArCH$_a$*H*$_b$, *H*-7$_b$), 3.19 (1H, app d, *J* 10.0Hz, O=CC*H*, *H*-15), 3.31 (1H, dd, *J* 10.0 and 3.0Hz, ArC*H*, *H*-14), 4.71 (1H, br s, O*H*), 6.62 (1H, d, *J* 2.5Hz, HOCC*H*C, *H*-9), 6.66 (1H, dd, *J* 8.5 and 2.5Hz, HOCC*H*CH, *H*-11), 6.89 (1H, s, PhC*H*=, *H*-19), 7.11 (1H, d, *J* 8.5Hz, HOCCHC*H*, *H*-12), 7.27–7.36 (3H, m, 3 x Ph*H*, *H*-21,23), 7.42 (2H, app d, *J* 7.5Hz, 2 x Ph*H*, *H*-22); (minor diastereoisomer) 1.26 (3H, s, C*H*$_3$, *H*-18), 1.47–1.81 (6H, m), 1.95–2.13 (3H, m)(*H*-1,2,3,5,6), 2.79 (1H, app d, *J* 10.0Hz, O=CC*H*, *H*-15), 2.93–2.99 (2H, m, ArC*H*$_2$, *H*-7), 3.30 (1H, dd, *J* 10.0 and 2.0Hz, ArC*H*, *H*-14), 5.25 (1H, br s, O*H*), 6.59 (1H, d, *J* 2.5Hz, HOCC*H*C, *H*-9), 6.65 (1H, dd, *J* 8.5 and 2.5Hz, HOCC*H*CH, *H*-11), 6.71 (1H, s, PhC*H*=, *H*-19), 6.92 (1H, d, *J* 8.5Hz, HOCCHC*H*, *H*-12), 7.25–7.39 (5H, m, 5 x Ph*H*, *H*-21,22,23); δ_C (100MHz, $CDCl_3$), (major diastereoisomer) 21.4 (t, *C*-2), 24.7 (t, *C*-6), 24.9 (t, *C*-1), 27.6 (q, *C*-18), 31.0 (t, *C*-7), 36.1 (d, *C*-14), 37.0 (t, *C*-3), 43.5 (s, *C*-4), 45.7 (d, *C*-5), 52.6 (d, *C*-15), 113.7 (d, *C*-11), 114.8 (d, *C*-9), 127.8 (2C d, *C*-21), 127.9 (d, *C*-23), 128.7 (d, *C*-12), 128.8 (s, *C*-13), 129.0 (2C d, *C*-22), 135.4 (d, *C*-19), 137.0 (s, *C*-20), 141.0 (s, *C*-8), 144.0 (s, *C*-17), 153.3 (s, *C*-10), 205.9 (s, *C*-16); (minor

diastereoisomer) 21.8 (t, *C*-2), 23.8 (t, *C*-6), 24.3 (q, *C*-18), 25.9 (t, *C*-1), 28.9 (t, *C*-7), 40.7 (s, *C*-4), 43.0 (d, *C*-14), 46.0 (t, *C*-3), 46.8 (d, *C*-5), 47.3 (d, *C*-15), 112.3 (d, *C*-11), 115.7 (d, *C*-9), 127.7 (s, *C*-13), 127.8 (2C d, *C*-21), 128.0 (d, *C*-23), 128.7 (d, *C*-12), 128.9 (2C d, *C*-22), 135.3 (d, *C*-19), 138.1 (s, *C*-20), 139.3 (s, *C*-8), 144.5 (s, *C*-17), 154.1 (s, *C*-10), 206.7 (s, *C*-16); m/z (ES) 359.1999 ($M + H^+$, $C_{25}H_{27}O_2$ requires 359.2006).

***(±)-Methylidene substituted methoxy bridged tricycle* 155**

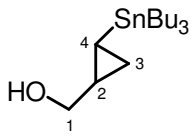


155

A solution of tri-*n*-butyltin hydride (107µl, 0.40mmol) and 2,2'-azobis(isobutyronitrile) (6mg, 0.04mmol) in degassed heptane (14ml), was added dropwise over 8h *via* syringe pump, to a stirred solution of the iodide **147** (140mg, 0.33mmol) and 2,2'-azobis(isobutyronitrile) (35mg, 0.21mmol) in degassed heptane (140ml), at 90°C under an argon atmosphere. The mixture was heated under reflux for a further 12h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (2–10% Et_2O, 98-90% petrol) to give the bridged tricyclic ketone **155** (18mg, 18%) as an inseparable mixture of diastereoisomers in a 2:1 ratio, as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 1695 (s), 1611 (s); δ_H (400MHz, $CDCl_3$), (major diastereoisomer) 1.31 (3H, s, CH_3, *H*-18), 1.50–1.83 (6H, m), 1.98–2.14 (3H, m)(*H*-1,2,3,5,6), 2.62 (1H, app td, *J* 14.5 and 3.0Hz, ArCH_aH_b, *H*-7_a), 2.86 (1H, app dt, *J* 14.5 and 3.5Hz, ArCH_aH_b, *H*-7_b), 3.21 (1H, app dd, *J* 9.0 and 3.0Hz, and 2.5Hz, O=C*CH*, *H*-15), 3.32 (1H, dd, *J* 10.5 and

3.0Hz, ArC*H*, *H*-14), 3.79 (3H, s, OCH_3, *H*-20), 5.43 (1H, d, *J* 1.0Hz, =CH_aH$_b$, *H*-19$_a$), 6.23 (1H, d, *J* 1.0Hz, =CH$_a$$H_b$, *H*-19$_b$), 6.69 (1H, d, *J* 2.5Hz, CH_3OCC*H*C, *H*-9), 6.75 (1H, dd, *J* 8.5 and 2.5Hz, CH_3OCC*H*CH, *H*-11), 7.16 (1H, d, *J* 8.5Hz, CH_3OCCHC*H*, *H*-12); (minor diastereoisomer) 1.20 (3H, s, CH_3, *H*-18), 1.55–1.95 (6H, m), 1.98–2.18 (3H,m)(*H*-1,2,3,5,6), 2.52 (1H, app d, *J* 9.0Hz, O=CC*H*, *H*-15), 2.95 (2H, app t, *J* 8.5Hz, ArCH_2, *H*-7), 3.26 (1H, dd, *J* 9.0 and 1.5Hz, ArC*H*, *H*-14), 3.78 (3H, s, OCH_3, *H*-20), 5.33 (1H, d, *J* 1.0Hz, =CH_aH$_b$, *H*-19a), 6.19 (1H, d, *J* 1.0Hz, =CH$_a$$H_b$, *H*-19b), 6.68 (1H, d, *J* 3.0Hz, CH_3OCC*H*C, *H*-9), 6.76 (1H, dd, *J* 8.0 and 3.0Hz, CH_3OCC*H*CH, *H*-11), 6.98 (1H, d, *J* 8.0Hz, CH_3OCCHC*H*, *H*-12); δ_C (100MHz, $CDCl_3$), (major diastereoisomer) 21.5 (t, *C*-2), 23.4 (t, *C*-6), 24.8 (t, *C*-1), 27.0 (q, *C*-18), 31.1 (t, *C*-7), 36.2 (d, *C*-14), 37.0 (t, *C*-3), 43.4 (s, *C*-4), 44.3 (d, *C*-5), 51.2 (d, *C*-15), 55.2 (q, *C*-20), 112.3 (d, *C*-11), 113.3 (d, *C*-9), 119.0 (t, *C*-19), 128.3 (d, *C*-12), 128.6 (s, *C*-13), 140.9 (s, *C*-8), 148.5 (s, *C*-17), 157.4 (s, *C*-10), 205.2 (s, *C*-16); (minor diastereoisomer) 21.8 (t, *C*-2), 22.3 (t, *C*-6), 24.4 (q, *C*-18), 25.9 (t, *C*-1), 29.1 (t, *C*-7), 40.1 (s, *C*-4), 41.7 (d, *C*-14), 44.7 (t, *C*-3), 46.1 (d, *C*-5), 46.5 (d, *C*-15), 55.3 (q, *C*-20), 110.6 (d, *C*-11), 114.4 (d, *C*-9), 119.7 (t, *C*-19), 127.8 (d, *C*-12), 131.6 (s, *C*-13), 138.7 (s, *C*-8), 146.2 (s, *C*-17), 158.0 (s, *C*-10), 205.3 (s, *C*-16); m/z (ES) 319.1669 (M + Na^+, $C_{20}H_{24}O_2Na$ requires 319.1674).

***[2E-(Tributylstannyl)cyclopropyl]methanol* 182**

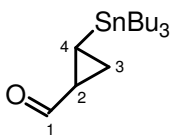


182

Diethylzinc (1.1M in Tol, 32ml, 35mmol) was added dropwise over 10 min, to a stirred solution of (*E*)-3-(tributylstannyl)prop-2-en-1-ol **181** (6.09g, 18mmol)[117]

and diiodomethane (4.2ml, 52mmol) in dichloromethane (250ml) at -50°C, under a nitrogen atmosphere. The solution was warmed slowly to -20°C over 2h and stirred at this temperature for a further 48h, before triethylamine (20ml) was added. After warming to room temperature, water (100ml) was added and the separated aqueous phase was then extracted with dichloromethane (3 x 100ml). The combined organic extracts were washed with brine (20ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc, 90% petrol) on silica gel, to give the cyclopropane **182** (4.66g, 74%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3611 (br m), 3029 (m); δ_H (400MHz, $CDCl_3$), 0.29–0.36 (1H, m, SnC*H*, *H*-4), 0.50-0.55 (2H, m, CHCH_2CH, *H*-3), 0.81 (6H, t, J 8.0Hz, SnCH_2, *H*-5), 0.89 (9H, t, *J* 7.5Hz, CH_2CH_3, H-8), 1.02–1.14 (1H, m, $HOCH_2CH$, *H*-2), 1.24–1.36 (6H, m, CH_3CH_2, *H*-7), 1.41–1.56 (6H, m, $SnCH_2CH_2$, *H*-6), 3.39 (1H, dd, *J* 10 and 7.5Hz, $HOCH_aH_b$, *H*-1_a), 3.55 (1H, dd, *J* 10 and 6.5Hz, $HOCH_aH_b$, *H*-1_b); δ_C (100MHz, $CDCl_3$), -2.6 (d, *C*-4), 7.4 (t, *C*-3), 8.7 (t, *C*-5), 13.7 (q, *C*-8), 18.1 (d, *C*-2), 27.3 (t, *C*-7), 29.1 (t, *C*-6), 69.6 (t, *C*-1); m/z (ES) 385.1539 ($M + Na^+$, $C_{16}H_{34}O^{120}SnNa$ requires 385.1529). This data agrees with that previously published for the chiral material.[118]

2E-(Tributylstannyl)cyclopropanecarbaldehyde **183**

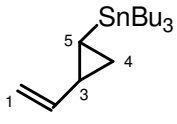


183

2-Iodoxybenzoic acid (5.0g, 17.9mmol) was added portionwise, to a stirred solution of the alcohol **182** (4.0g, 11.1mmol) in dimethylsulfoxide (80ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at

room temperature for 20h, then water (40ml) was added and the resulting precipitate was filtered through celite with diethyl ether (50ml). The separated aqueous phase was extracted with diethyl ether (3 x 20ml) and the combined organic extracts were washed with brine (10ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O, 80% petrol) on silica gel, to give the aldehyde **183** (3.8g, 96%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3029 (s), 1696 (s); δ_H (400MHz, $CDCl_3$), 0.58 (1H, ddd, *J* 11.0, 8.5 and 5.5Hz, SnC*H*, *H*-4), 0.88 (6H, t, *J* 8.5Hz, SnCH_2, *H*-5), 0.89 (9H, t, *J* 7.0Hz, CH_2CH_3, H-8), 1.04 (1H, ddd, *J* 8.5, 7.0 and 4.5Hz, CHCH_aH$_b$CH, *H*-3$_a$), 1.24–1.37 (7H, m, CHCH$_a$$H_b$CH + CH_3CH_2, *H*-3$_b$,7), 1.43–1.54 (6H, m, $SnCH_2CH_2$, *H*-6), 1.68-1.76 (1H, m, O=CHC*H*, *H*-2), 8.52 (1H, d, *J* 6.5Hz, O=C*H*, *H*-1); δ_C (100MHz, $CDCl_3$), 1.7 (d, *C*-4), 9.0 (t, *C*-5), 11.2 (t, *C*-3), 13.7 (q, *C*-8), 26.9 (d, *C*-2), 27.3 (t, *C*-7), 28.9 (t, *C*-6), 201.6 (d, *C*-1); m/z (ES) 383.1359 (M + Na^+, $C_{16}H_{32}O^{120}SnNa$ requires 383.1373).

Tributyl(2-vinyl-E-cyclopropyl)stannane **168**

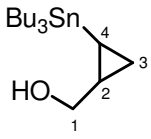


168

Tetrahydrofuran (60ml) was added to freshly dried (100°C, 1mmHg, 5h) methyltriphenylphosphonium bromide (7.0g, 19.6mmol) at room temperature. Sodium hexamethyldisilazane (2.0M in THF, 6.0ml, 12.0mmol) was added dropwise over 10 min, to the stirred solution at -78°C, under a nitrogen atmosphere. The yellow solution was stirred at -78°C for 30 min and then a solution of the aldehyde **183** (3.4g, 9.5mmol) in tetrahydrofuran (30ml) was

added dropwise over 5 min. The mixture was stirred at -78°C for 2h and then allowed to warm to room temperature over 12h. Saturated aqueous ammonium chloride solution (10ml) was added, and the separated aqueous phase was then extracted with diethyl ether (3 x 20ml). The combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the alkene **168** (3.3g, 97%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3083 (w), 1631 (m); δ_H (400MHz, $CDCl_3$), 0.11 (1H, ddd, *J* 10.5, 8.5 and 5.5Hz, SnC*H*, *H*-5), 0.70-0.76 (2H, m, CHCH_2CH, *H*-4), 0.81 (6H, t, *J* 8.0Hz, SnCH_2, *H*-6), 0.89 (9H, t, *J* 7.5Hz, CH_2CH_3, *H*-9), 1.25–1.36 (6H, m, CH_3CH_2, *H*-8), 1.36–1.44 (1H, m, H_2C=CHC*H*, *H*-3), 1.44-1.56 (6H, m, $SnCH_2CH_2$, *H*-7), 4.80 (1H, dd, *J* 10.0 and 1.5Hz, H_aH_bC=CH, *H*-1_a), 5.05 (1H, dd, *J* 17.0 and 1.5Hz, H_aH_bC=CH, *H*-1_b), 5.29 (1H, ddd, *J* 17.0, 10.0 and 9.0Hz, H_2C=C*H*, *H*-2); δ_C (100MHz, $CDCl_3$), 2.6 (d, *C*-5), 8.7 (t, *C*-6), 11.5 (t, *C*-4), 13.7 (q, *C*-9), 19.4 (d, *C*-3), 27.3 (t, *C*-8), 29.1 (t, *C*-7), 110.5 (t, *C*-1), 144.6 (d, *C*-2); m/z (EI) 301.0986 (M – Bu, $C_{13}H_{25}{}^{120}Sn$ requires 301.0978).

[2Z-(Tributylstannyl)cyclopropyl)methanol **182Z**

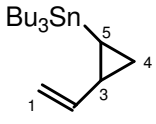


182Z

Diethylzinc (1.0M in hexanes, 5.8ml, 5.8mmol) was added dropwise over 10 min, to a stirred solution of (*Z*)-3-(tributylstannyl)prop-2-en-1-ol **181Z** (1.0g, 2.9mmol)[119] and diiodomethane (0.9ml, 11.1mmol) in dichloromethane (100ml) at -50°C, under a nitrogen atmosphere. The solution was warmed slowly to -20°C over 2h and stirred at this temperature for a further 48h, before

triethylamine (20ml) was added. After warming to room temperature, water (50ml) was added and the separated aqueous phase was then extracted with dichloromethane (3 x 20ml). The combined organic extracts were washed with brine (20ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc, 90% petrol) on silica gel, to give the cyclopropane **182Z** (0.8g, 78%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3610 (br m), 3053 (w); δ_H (400MHz, $CDCl_3$), -0.02 (1H, ddd, *J* 9.5, 9.0 and 7.5Hz, CHC*H*$_a$H$_b$CH, *H*-3$_a$), 0.20 (1H, ddd, J 7.5, 4.0 and 3.5Hz, CHCH$_a$*H*$_b$CH, *H*-3$_b$), 0.81-0.86 (6H, m, SnC*H*$_2$, *H*-5), 0.86-0.93 (10H, m, SnC*H* + CH$_2$C*H*$_3$, *H*-4,8), 1.26–1.41 (7H, m, CH$_3$C*H*$_2$ + HOCH$_2$C*H*, *H*-2,7), 1.44–1.54 (6H, m, SnCH$_2$C*H*$_2$, *H*-6), 3.25 (1H, ddd, *J* 11.0,8.0 and 3.5Hz, HOC*H*$_a$H$_b$, *H*-1$_a$), 3.56 (1H, app dt, *J* 11.0 and 5.5Hz, HOCH$_a$*H*$_b$, *H*-1$_b$); δ_C (100MHz, $CDCl_3$), -1.3 (d, *C*-4), 7.2 (t, *C*-3), 9.8 (t, *C*-5), 13.7 (q, *C*-8), 17.5 (d, *C*-2), 27.4 (t, *C*-7), 29.1 (t, *C*-6), 68.6 (t, *C*-1); m/z (ES) 385.1511 (M + Na^+, $C_{16}H_{34}O^{120}SnNa$ requires 385.1524).

Tributyl(2-vinyl-Z-cyclopropyl)stannane **168Z**



168Z

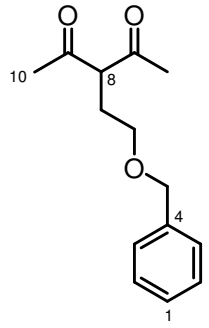
2-Iodoxybenzoic acid (6.5g, 23.2mmol) was added portionwise, to a stirred solution of the alcohol **182Z** (5.6g, 15.5mmol) in dimethylsulfoxide (100ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 12h, then water (50ml) was added and the resulting precipitate was filtered through celite with diethyl ether (50ml). The separated aqueous phase was extracted with diethyl ether (3 x 20ml) and the combined

organic extracts were washed with brine (10ml) and then dried over sodium sulphate. The solution was filtered through a short plug of silica and concentration *in vacuo* to leave the aldehyde **183Z** (4.4g, 79%) as a colourless oil. Due to its poor stability, the aldehyde was taken onto the next reaction immediately.

Tetrahydrofuran (100ml) was added to freshly dried (100°C, 1mmHg, 5h) methyltriphenylphosphonium bromide (9.9g, 27.7mmol) at room temperature. Sodium hexamethyldisilazane (2.0M in THF, 8.4ml, 16.8mmol) was added dropwise over 10 min, to the stirred solution at -78°C, under a nitrogen atmosphere. The yellow solution was stirred at -78°C for 30 min and then a solution of the aldehyde **183Z** (4.4g, 12.3mmol) in tetrahydrofuran (40ml) was added dropwise over 10 min. The mixture was stirred at -78°C for 2h and then allowed to warm to room temperature over 12h. Saturated aqueous ammonium chloride solution (10ml) was added, and the separated aqueous phase was then extracted with petroleum ether (3 x 30ml). The combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the alkene **168Z** (3.0g, 74%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3084 (w), 1633 (m); δ_H (400MHz, $CDCl_3$), 0.22 (1H, ddd, *J* 13.5, 9.0 and 8.0Hz, SnC*H*, *H*-5), 0.44 (1H, app dt, *J* 8.0 and 4.0Hz, CHC$H_a$$H_b$CH, *H*-$4_a$), 0.81 (6H, t, *J* 8.0Hz, SnCH_2, *H*-6), 0.89 (9H, t, *J* 7.5Hz, CH_2CH_3, *H*-9), 1.07 (1H, ddd, J 9.0, 4.5 and 4.0Hz CHC$H_a$$H_b$CH, *H*-$4_b$), 1.25–1.37 (6H, m, CH_3CH_2, *H*-8), 1.45-1.55 (6H, m, $SnCH_2CH_2$, *H*-7), 1.71 (1H, app dtd, J 13.5, 9.0 and 4.0Hz, H_2C=CHC*H*, *H*-3), 4.86 (1H, dd, *J* 10.0 and 2.0Hz, $H_a$$H_b$C=CH, *H*-$1_a$), 5.10 (1H, dd, *J* 17.0 and 2.0Hz, $H_a$$H_b$C=CH, *H*-$1_b$), 5.29 (1H, ddd, *J* 17.0, 10.0 and 9.0Hz, H_2C=C*H*, *H*-

2); δ_C (100MHz, $CDCl_3$), 3.7 (d, *C*-5), 9.7 (t, *C*-6), 10.6 (t, *C*-4), 13.7 (q, *C*-9), 18.6 (d, *C*-3), 27.3 (t, *C*-8), 29.1 (t, *C*-7), 112.2 (t, *C*-1), 143.9 (d, *C*-2); m/z (EI) 301.0980 (M – Bu, $C_{13}H_{25}{}^{120}Sn$ requires 301.0978).

3-(2-(Benzyloxy)ethyl)pentane-2,4-dione **192**

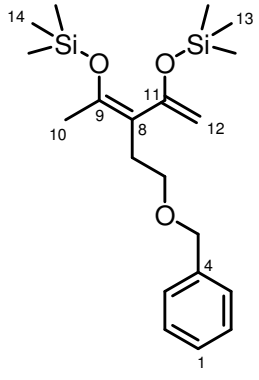


192

Potassium carbonate (32g, 232mmol) was added in one portion, to a stirred solution of pentane-2,4-dione (20g, 200mmol) and 1-((2-iodoethoxy)methyl) benzene[120] (5g, 19mmol) in freshly distilled acetone (150ml) at room temperature, under a nitrogen atmosphere. The mixture was heated under reflux for 48h and then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc, 90% petrol) on silica gel, to give the ketone **192** (3.4g, 64% (98% BRSM)) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2863 (m), 1695 (s), δ_H (400MHz, $CDCl_3$), (exists as a 3:2 mixture of Keto-enol forms) (Keto) 2.16-2.20 (2H, m, OCH_2CH_2, *H*-7), 2.19 (6H, s, O=CCH_3, *H*-10), 3.48 (2H,t, *J* 5.5Hz, OCH_2CH_2, *H*-6), 3.85 (1H, t, *J* 7.0Hz, O=CC*H*, *H*-8), 4.43 (2H, s, $PhCH_2$, *H*-5), 7.26-7.36 (5H, m, 5 x Ph*H*, *H*-1,2,3); (Enol) 2.16 (6H, s, 2 x CH_3, *H*-10), 2.56 (2H, t, *J* 7.0Hz, OCH_2CH_2, *H*-7), 3.49 (2H, t, *J* 7.0Hz, OCH_2CH_2, *H*-6), 4.51 (2H, s, $PhCH_2$, *H*-5), 7.26-7.36 (5H, m, 5 x Ph*H*, *H*-1,2,3); δ_C (100MHz, $CDCl_3$) (Oxo) 28.5 (t, *C*-7), 29.4 (q, *C*-10), 65.8 (d, *C*-8), 67.7 (t, *C*-6), 73.1 (t, *C*-5), 127.7 (2C d, *C*-3), 127.8 (d, *C*-1),

128.5 (2C d, *C*-2), 138.0 (s, *C*-4), 204.2 (s, *C*-9); (Enol) 23.1 (q, *C*-10), 28.1 (t, *C*-7), 69.9 (t, *C*-6), 73.1 (t, *C*-5), 106.8 (s, *C*-8), 127.5 (2C d, *C*-3), 127.7 (d, *C*-1), 127.8 (2C d, *C*-2), 138.2 (s, *C*-4), 191.8 (s, *C*-9); m/z (ES) 257.1146 (M + Na^+, $C_{14}H_{18}O_3Na$ requires 257.1148).

((E/Z)-3-(2-(Benzyloxy)ethyl)penta-2,4-dien-2,4-yloxy)-bis-trimethylsilane **191**

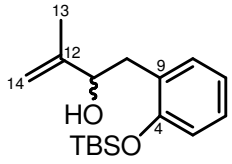


191

Freshly distilled trimethylsilyl chloride (1.64ml, 12.8mmol) was added dropwise, over 5min, to a stirred solution of anhydrous LiBr (1.49g, 17.1mmol) in tetrahydrofuran (5ml) at -20°C, under a nitrogen atmosphere. A solution of the 1,3-dione **192** (1g, 4.3mmol) in tetrahydrofuran (2ml), and distilled triethylamine (1.8ml, 12.9ml), were then added sucessively, *via* cannula over 5 mins, to the stirred mixture at -20°C. The mixture was stirred for 1h at -20°C before being warmed to 40°C and stirred for a further 48h. The mixture was cooled to 0°C, then cold pentane (10ml) was added and the mixture was poured onto a cold solution of saturated sodium hydrogen carbonate (20ml). The separated aqueous phase was extracted with cold pentane (3 x 5ml) and the combined organic extracts were then dried over sodium sulphate and concentrated *in vacuo* to leave the *bis*-enol ether **191** (1.59g, 99%) as a slightly yellow oil; (the compound was unstable to acid and moisture) δ_H (400MHz, C_6D_6) (a 2:1 mixture of *E*:*Z* isomers) (*E*) 0.20, 0.26 (18H, 2 x s, 2 x Si(CH_3)$_3$,

H-13,14), 2.08 (3H, s, C=CCH_3, *H*-10), 2.97 (2H, t, *J* 7.5Hz, OCH$_2$CH_2, *H*-7), 3.80 (2H, t, *J* 7.5Hz, OCH_2CH$_2$, *H*-6), 4.34 (1H, s, C=CH_aH$_b$, *H*-12$_a$), 4.54 (2H, s, PhCH_2, *H*-5), 4.57 (1H, s, C=CH$_a$$H_b$, *H*-12$_b$), 7.13-7.43 (5H, m, 5 x Ph*H*, *H*-1,2,3); (*Z*) 0.24, 0.29 (18H, 2 x s, 2 x Si(CH_3)$_3$, *H*-13,14), 1.85 (3H, s, C=CCH_3, *H*-10), 2.70 (2H, t, *J* 7.5Hz, OCH$_2$CH_2, *H*-7), 3.68 (2H, t, *J* 7.5Hz, OCH_2CH_2, *H*-6), 4.49 (2H, s, PhCH_2, *H*-5), 4.64 (1H, s, C=CH_aH$_b$, *H*-12$_a$), 4.80 (1H, s, C=CH$_a$$H_b$, *H*-12$_b$), 7.13-7.43 (5H, m, 5 x Ph*H*, *H*-1,2,3); δ_C (100MHz, C_6D_6) (*E*) 0.2, 0.8 (2 x q, *C*-13,14), 20.7 (q, *C*-10), 29.0 (t, *C*-7), 69.4 (t, *C*-6), 72.9 (t, *C*-5), 95.1 (t, *C*-12), 116.8 (s, *C*-8), 127.4, 127.9, 128.4 (3 x d, *C*-1,2,3), 139.7 (s, *C*-4), 147.7 (s, *C*-9), 157.2 (s, *C*-11); (*Z*) 0.3, 0.8 (2 x q, *C*-13,14), 19.8 (q, *C*-10), 30.5 (t, *C*-7), 70.1 (t, *C*-6), 73.0 (t, *C*-5), 95.0 (t, *C*-12), 114.7 (s, *C*-8), 127.3, 128.1, 128.5 (3 x d, *C*-1,2,3), 139.6 (s, *C*-4), 146.8 (s, *C*-9), 154.8 (s, *C*-11).

***(±)-2-(2-(tert-Butyldiphenylsilanyloxy)-3-methylbut-3-enyl)phenol* 208**



208

A solution of potassium permanganate (0.4g, 2.5mmol) in water (1.5ml) was added dropwise over 10min to a stirred solution of (2-allylphenoxy)(*tert*-butyl)dimethylsilane (0.25g, 1.1mmol)[121] in isopropyl alcohol (3.5ml), (until TLC showed no remaining olefin). A solution of periodic acid (0.45g, 2.0mmol) in water (0.5ml) was added quickly, in one portion, and the mixture was then stirred until TLC showed no remaining diol (approximately 15mins). The mixture was poured onto water (10ml) and extracted with ethyl acetate (3 x 20ml). The combined organic extracts were washed with saturated sodium

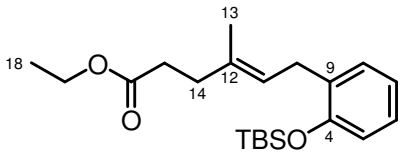
hydrogen carbonate solution (50ml), dried over sodium sulphate and concentrated *in vacuo* to leave the crude aldehyde **204** an unstable oil which was used immediately in the next step without further purification; δ_H (400MHz, $CDCl_3$), 0.25 (6H, s, OSi(C*H*$_3$)$_2$, *H*-3), 0.99 (9H, s, OSiC(C*H*$_3$)$_3$, *H*-1), 3.63 (2H, d, *J* 2.0Hz, ArC*H*$_2$, *H*-10), 6.90 (1H, dd, *J* 8.0 and 1.0Hz, Ar*H*, *H*-5), 6.95 (1H, ddd, *J* 7.5, 7.5 and 1.0Hz, Ar*H*, *H*-7), 7.15 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-8), 7.19 (1H, ddd, *J* 8.0, 7.5 and 1.5Hz, Ar*H*, *H*-6), 9.69 (1H, t, *J* 2.0Hz, O=C*H*, *H*-11).

Boron trifluoride etherate (4.4ml, 35mmol) was added dropwise over 2 min, to a stirred solution of the crude aldehyde **204** (8g, 34mmol) in tetrahydrofuran (200ml) at -78^{o}C, under a nitrogen atmosphere. The mixture was stirred at -78^{o}C for 10mins and then a solution of isopropylmagnesium bromide (0.5M in THF, 82ml, 41mmol) was added dropwise over 20 min, at -78^{o}C. The mixture was allowed to warm to room temperature over 2h, and then saturated ammonium chloride solution (20ml) and ethyl acetate (20ml) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were then washed with brine (20ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (4% EtOAc, 96% petrol) on silica gel, to give the alcohol **208** (4.45g, 45%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3487 (br m), 2930 (s), 1453 (m); δ_H (400MHz, $CDCl_3$), 0.27 (6H, s, OSi(C*H*$_3$)$_2$, *H*-3), 1.03 (9H, s, OSiC(C*H*$_3$)$_3$, *H*-1), 1.82 (3H, s, C=CC*H*$_3$, *H*-13), 2.13 (1H, d, *J* 3.0Hz, O*H*), 2.78 (1H, dd, *J* 13.5 and 9.5Hz, ArC*H*$_a$H$_b$, *H*-10$_a$), 2.93 (1H, dd, *J* 13.5 and 4.0Hz, ArCH$_a$*H*$_b$, *H*-10$_b$), 4.31 (1H, ddd, *J* 9.5, 4.0 and 3.0Hz, HOC*H*, *H*-11), 4.85 (1H, app t, *J* 1.5Hz, C=C*H*$_a$H$_b$, *H*-14$_a$), 4.94 (1H, app t, *J* 1.0Hz,

C=CH_aH_b, *H*-14_b), 6.83 (1H, dd, *J* 8.0 and 1.0Hz, Ar*H*, *H*-5), 6.92 (1H, ddd, *J* 7.5, 7.5 and 1.0Hz, Ar*H*, *H*-7), 7.12 (1H, ddd, *J* 8.0, 7.5 and 1.5Hz, Ar*H*, *H*-6), 7.18 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-8); δ_C (100MHz, $CDCl_3$), -4.1 (2C q, *C*-3), 18.0 (q, *C*-13), 18.3 (s, *C*-2), 25.8 (3C q, *C*-1), 37.4 (t, *C*-10), 75.7 (d, *C*-11), 111.0 (t, *C*-14), 118.6 (d, *C*-5), 121.3 (d, *C*-7), 127.6 (d, *C*-6), 128.9 (s, *C*-9), 131.6 (d, *C*-8), 147.2 (s, *C*-12), 153.8 (s, *C*-4); m/z (ES) 315.1746 (M + Na^+, $C_{17}H_{18}O_2{}^{28}SiNa$ requires 315.1756).

(E)-Ethyl-6-(2-(tert-butyldiphenylsilanyloxy)phenyl)-4-methylhex-4-enoate

244

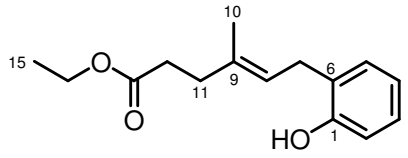


244

Propionic acid (0.04ml, 0.5mmol) was added dropwise over 2mins, to a stired solution of the alcohol **208** (0.78g, 0.3mmol) in triethyl orthoacetate (10ml, 54.6mmol) at room temperature under a nitrogen atmosphere. The solution was heated to 100°C for 5h, then cooled to room temperature and stirred overnight. The solution was concentrated *in vacuo* and then diethyl ether (20ml) and water (5ml) were added. The separated aqueous phase was extracted with diethyl ether (5 x 10ml) and the combined organic extracts were then washed with saturated sodium hydrogen carbonate solution (10ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% Et_2O, 95% petrol) on silica gel, to give the ester **244** (0.89g, 92%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2930 (s), 1726 (s), 1452 (m); δ_H (400MHz, $CDCl_3$), 0.23 (6H, s, OSi(CH_3)$_2$, *H*-3), 1.01 (9H, s, OSiC(CH_3)$_3$, *H*-1), 1.23 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-18), 1.70 (3H, app s, C=CCH_3, *H*-13), 2.33-2.46 (4H, m,

O=CCH_2CH_2, *H*-14,15), 3.31 (2H, d, *J* 7.0Hz, ArCH_2, *H*-10), 4.10 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-17), 5.36 (1H, tq, *J* 7.0 and 1.0Hz, C=C*H*, *H*-11), 6.78 (1H, dd, *J* 8.0 and 1.0Hz, Ar*H*, *H*-5), 6.87 (1H, ddd, *J* 7.5, 7.5 and 1.0Hz, Ar*H*, *H*-7), 7.03-7.10 (2H, m, 2 x Ar*H*, *H*-6,8); δ_C (100MHz, $CDCl_3$), -4.1 (2C q, *C*-3), 14.2 (q, *C*-18), 16.1 (q, *C*-13), 18.3 (s, *C*-2), 25.8 (3C q, *C*-1), 28.3 (t, *C*-10), 33.2 (t, *C*-15), 34.7 (t, *C*-14), 60.3 (t, *C*-17), 118.4 (d, *C*-5), 121.0 (d, *C*-7), 123.4 (d, *C*-11), 126.6 (d, *C*-6), 129.5 (d, *C*-8), 131.8 (s, *C*-9), 134.4 (s, *C*-12), 153.3 (s, *C*-4), 173.4 (s, *C*-16); m/z (ES) 385.2150 ($M + Na^+$, $C_{21}H_{34}O_3{}^{28}SiNa$ requires 385.2175).

***(E)-Ethyl 6-(2-hydroxyphenyl)-4-methylhex-4-enoate* 245**

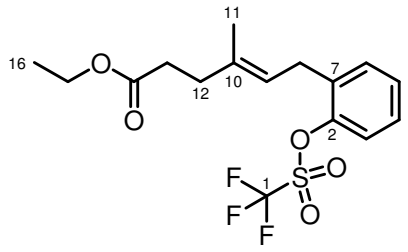


245

A solution of tetrabutylammonium fluoride (0.21g, 0.7mmol) in tetrahydrofuran (0.75ml) was added dropwise over 5mins, to a stirred solution of the TBS ether **244** (0.20g, 0.6mmol) in tetrahydrofuran (2ml) at room temperature, under a nitrogen atmosphere. The mixture was stirred until TLC showed no remaining ether (approximately 30mins), and then diethyl ether (5ml) and water (5ml) were added. The separated aqueous phase was extracted with diethyl ether (3 x 10ml) and the combined organic extracts were then washed with brine (10ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc, 90% petrol) on silica gel, to give the phenol **245** (0.14g, 99%) as an unstable colourless oil was taken through to the next step immediately; δ_H (400MHz, $CDCl_3$), 1.22 (3H, t, *J* 7.0Hz, OCH$_2$CH_3, *H*-15), 1.78 (3H, app s, C=CCH_3, *H*-10), 2.34-2.48 (4H, m,

O=CCH_2CH_2, *H*-11,12), 3.36 (2H, d, *J* 7.0Hz, ArCH_2, *H*-7), 4.10 (2H, q, *J* 7.0Hz, OCH_2CH$_3$, *H*-14), 4.99 (1H, s, OH), 5.36 (1H, tq, *J* 7.0 and 1.5Hz, C=C*H*, *H*-8), 6.79 (1H, dd, *J* 7.5 and 1.0Hz, Ar*H*, *H*-5), 6.86 (1H, ddd, *J* 7.5, 7.0 and 1.0Hz, Ar*H*, *H*-4), 7.06-7.13 (2H, m, 2 x Ar*H*, *H*-2,3).

***2-((E)-5-(Ethoxycarbonyl)-3-methylpent-2-enyl)phenyl trifluoromethanesulfonate* 246**

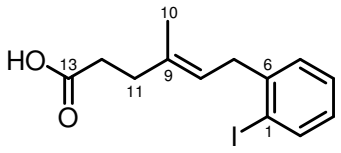


246

Trifluoromethanesulfonic anhydride (0.12ml, 4.7mmol) was added dropwise over 5mins, to a stirred solution of the phenol **245** (0.13g, 0.5mmol) in dichloromethane (1ml) and pyridine (1ml) at 0^{o}C, under a nitrogen atmosphere. The solution was warmed to room temperature overnight and then ethyl acetate (5ml) and water (5ml) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 10ml) and the combined organic extracts were then washed with hydrochloric acid (2M, 5ml), brine (10ml) and saturated copper sulphate solution (10ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOAc, 95% petrol) on silica gel, to give the triflate **246** (0.18g, 92%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2985 (s), 1727 (s); δ_H (400MHz, $CDCl_3$), 1.22 (3H, t, *J* 7.0Hz, OCH$_2$CH_3, *H*-16), 1.71 (3H, s, C=CCH_3, *H*-11), 2.34-2.47 (4H, m, O=CCH_2CH_2, *H*-12,13), 3.43 (2H, d, *J* 7.0Hz, ArCH_2, *H*-8), 4.09 (2H, q, *J* 7.0Hz, OCH_2CH$_3$, *H*-15), 5.29 (1H, t, *J* 7.0Hz, C=C*H*, *H*-9), 7.21-7.32 (4H, m, 4 x Ar*H*, *H*-3,4,5,6); δ_C

(100MHz, $CDCl_3$), 14.2 (q, *C*-16), 16.1 (q, *C*-11), 28.1 (t, *C*-8), 33.0 (t, *C*-13), 34.5 (t, *C*-12), 60.3 (t, *C*-15), 120.2 (q, *C*-1), 121.0, 121.2 (2 x d, C-3,5), 127.7 (d, C-9), 128.4 (d, C-4), 130.9 (d, C-6), 134.0 (s, *C*-7), 136.6 (s, *C*-10), 147.9 (s, *C*-2), 173.2 (s, *C*-14); m/z (ES) 403.0803 (M + Na^+, $C_{16}H_{19}O_5{}^{32}S{}^{19}F_3Na$ requires 403.0803).

***(E)-6-(2-Iodophenyl)-4-methylhex-4-enoic acid* 247**

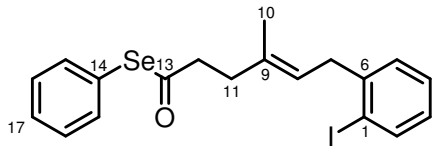


247

A solution of lithium hydroxide (47mg, 1.1mmol) in water (3ml) was added, in one portion, to a stirred solution of the ester **210** (100mg, 0.3mmol) in ethanol (2ml) and tetrahydrofuran (8ml) at room temperature. The mixture was stirred at room temperature for 12h and then concentrated *in vacuo*. Diethyl ether (5ml) and saturated sodium hydrogen carbonate (5ml) were added and the separated organic phase was then extracted with water (3 x 5ml). Hydrochloric acid (2M) was added to the combined aqueous extracts until pH 1 (approximately 25ml). The acidified aqueous phase was extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were then dried over sodium sulphate and concentrated *in vacuo* to leave the acid **247** (80mg, 90%) as a colourless oil, which was used in the next step without further purification; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2924 (br m), 1710 (s); δ_H (400MHz, $CDCl_3$), 1.74 (3H, app s, C=CC*H*$_3$, *H*-10), 2.39 (2H, m, O=CCH$_2$C*H*$_2$, *H*-11), 2.51 (2H, m, O=CC*H*$_2$CH$_2$, *H*-12), 3.42 (2H, d, *J* 7.0Hz, ArC*H*$_2$, *H*-7), 5.33 (1H, tq, *J* 7.0 and 1.5Hz, C=C*H*, *H*-8), 6.88 (1H, ddd, *J* 8.0, 7.0 and 2.0Hz, Ar*H*, *H*-3), 7.16 (1H, dd, *J* 7.5 and 2.0Hz, Ar*H*, *H*-5), 7.26 (1H, ddd, *J* 7.5, 7.0 and 1.5Hz, Ar*H*, *H*-4), 7.81 (1H, dd,

J 8.0 and 1.5Hz, Ar*H*, *H*-2);); δ_C (100MHz, $CDCl_3$), 16.5 (q, C-10), 32.6 (t, C-12), 34.3 (t, C-11), 39.5 (t, C-7), 100.8 (s, C-1), 122.7 (d, C-8), 127.7 (d, C-3), 128.3 (d, C-4), 129.2 (d, C-5), 135.2 (s, C-9), 139.4 (d, C-2), 143.7 (s, C-6), 178.7 (s, C-13); m/z (ES) 352.9984 (M + Na^+, $C_{13}H_{15}O_2{}^{127}INa$ requires 353.0014).

***(E)-6-(2-Iodophenyl)-4-methylhex-4-enoyl benzeneselenenate* 248**

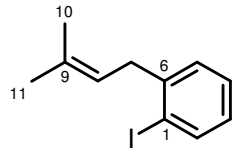


248

Tributylphosphine (125µl, 0.5mmol) was added dropwise over 5mins, to a stirred solution of the acid **247** (80mg, 0.3mmol) in dichloromethane (15ml) at -40°C, under an argon atmosphere. After stirring for 5mins, *N*-phenylselenylphthalimide (150mg, 0.5mmol) was added in one portion at -40°C. The mixture was stirred at -40°C for 1h then poured onto water (5ml) and diluted with dichloromethane (5ml). The separated aqueous phase was extracted with dichloromethane (3 x 10ml) and the combined organic extracts were then washed with saturated sodium hydrogen carbonate (10ml),dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the selenyl ester **248** (53mg, 46%) as a yellow oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2925 (m), 1719 (s); δ_H (400MHz, $CDCl_3$), 1.77 (3H, app s, C=CCH_3, *H*-10), 2.47 (2H, t, *J* 7.0Hz, O=CCH_2CH_2, *H*-11), 2.88 (2H, t, *J* 7.0Hz, O=CC$H_2$$CH_2$, *H*-12), 3.45 (2H, d, *J* 7.5Hz, ArCH_2, *H*-7), 5.36 (1H, tq, *J* 7.5 and 1.0Hz, C=C*H*, *H*-8), 6.92 (1H, ddd, *J* 8.0, 7.0 and 1.5Hz, Ar*H*, *H*-3), 7.19 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-5), 7.28 (1H, ddd, *J* 7.5, 7.0 and 1.5Hz, Ar*H*, *H*-4), 7.39 (3H, m, 3 x Ph*H*, *H*-16,17),

7.51 (2H, dd, *J* 7.5 and 1.0Hz, 2 x Ph*H*, *H*-15), 7.85 (1H, dd, *J* 8.0 and 1.5Hz, Ar*H*, *H*-2); δ_C (100MHz, $CDCl_3$), 16.5 (q, C-10), 34.9 (t, C-11), 39.5 (t, C-7), 46.0 (t, C-12), 100.8 (s, C-1), 123.2 (d, C-8), 126.4 (s, C-14), 127.8 (d, C-3), 128.3 (d, C-4), 128.8 (d, C-5), 129.2 (2C d, C-16), 129.3 (d, C-17), 134.7 (s, C-9), 135.8 (2C d, C-15), 139.4 (d, C-2), 143.7 (s, C-6), 199.7 (s, C-13); m/z (ES) 492.9539 ($M + Na^+$, $C_{19}H_{19}O^{127}I^{80}SeNa$ requires 492.9544).

1-Iodo-2-(3-methylbut-2-enyl)benzene **216**

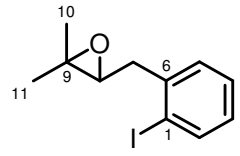


216

Tetrahydrofuran (2ml) was added to a flask containing dried (high vacuum at 80°C for 1h) isopropyltriphenylphosphonium iodide (0.35g, 0.8mmol) at room temperature, under an argon atmosphere. *n*-Butyllithium (2.5M, 0.28ml, 0.7mmol) was added dropwise over 5mins, to the stirred solution at 0°C, and the mixture was then stirred at 0°C for 30mins. A solution of 2-(2-iodophenyl)acetaldehyde[122] **212** (0.10g, 0.4mmol) in tetrahydrofuran (2ml) was added dropwise over 5mins, at 0°C and the mixture was stirred at 0°C for a 3h and then diethyl ether (5ml) and water (5ml) were added. The separated aqueous phase was extracted with diethyl ether (5 x 5ml) and the combined organic extracts were then washed with brine (10ml), dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the olefin **216** (0.10g, 82%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2916 (s), 1562 (m); δ_H (400MHz, $CDCl_3$), 1.76 (3H, s, C=C(CH_{3E})CH_{3Z}, *H*-11), 1.77 (3H, d, *J* 1.0Hz, C=C(CH_{3E})CH_{3Z}, *H*-10), 3.42 (2H, d, *J* 7.0Hz, ArCH_2, *H*-7), 5.27 (1H, tq, *J* 7.0 and 1.0Hz, $(CH_3)_2$C=C*H*, *H*-

8), 6.88 (1H, ddd, *J* 8.0, 7.5 and 2.0Hz, Ar*H*, *H*-3), 7.20 (1H, dd, *J* 7.5 and 2.0Hz, Ar*H*, *H*-5), 7.27 (1H, ddd, *J* 8.0, 7.5 and 1.0Hz, Ar*H*, *H*-4), 7.82 (1H, dd, *J* 7.5 and 1.0Hz, Ar*H*, *H*-2); δ_C (100MHz, $CDCl_3$), 18.2 (q, *C*-10), 25.8 (q, *C*-11), 39.7 (t, *C*-7), 100.8 (s, *C*-1), 121.7 (d, *C*-8), 127.6 (d, *C*-3), 128.3 (d, *C*-4), 129.3 (d, *C*-5), 133.6 (s, *C*-9), 139.4 (d, *C*-2), 144.3 (s, *C*-6); m/z (EI) 272.0069 ($C_{11}H_{13}{}^{127}I$ requires 272.0062).

***3-(2-Iodobenzyl)-2,2-dimethyloxirane* 217**

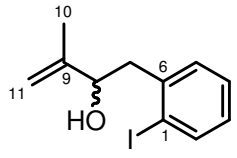


217

A solution of 3-chloroperbenzoic acid (75% in H_2O, 100mg, 0.4mmol) in dichloromethane (2ml) was added dropwise over 5mins, to a stirred solution of the olefin **216** (100mg, 0.4mmol) in dichloromethane (2ml) at 0°C, under a nitrogen atmosphere. The mixture was stirred at room temperature for 24h and then saturated sodium hydrogen carbonate (5ml) was added. The separated aqueous phase was extracted with dichloromethane (3 x 5ml) and the combined organic extracts were then washed with brine (10ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (100% petrol) on silica gel, to give the epoxide **217** (89mg, 84%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2965 (s); δ_H (400MHz, $CDCl_3$), 1.36 (3H, s, C=C(CH_{3E})CH_{3Z}, *H*-11), 1.42 (3H, s, C=C(CH_{3E})CH_{3Z}, *H*-10), 2.92-3.05 (3H, m, ArCH_2C*H*, *H*-7,8), 6.94 (1H, ddd, *J* 8.0, 7.0 and 2.0Hz, Ar*H*, *H*-3), 7.28-7.34 (2H, m, 2 x Ar*H*, *H*-4,5), 7.85 (1H, dd, *J* 8.0 and 1.0Hz, Ar*H*, *H*-2); δ_C (100MHz, $CDCl_3$), 19.1 (q, *C*-10), 24.8 (q, *C*-11), 40.0 (t, *C*-7), 58.7 (s, C-9), 63.4 (d, C-8), 100.8 (s, *C*-1), 128.3, 128.5 (2 x d, *C*-3,4), 129.6 (d, *C*-

5), 139.5 (d, *C*-2), 141.4 (s, *C*-6); m/z (ES) 310.9891 ($M + Na^+$, $C_{11}H_{13}O^{127}INa$ requires 310.9909).

***(±)-1-(2-Iodophenyl)-3-methylbut-3-en-2-ol* 211**

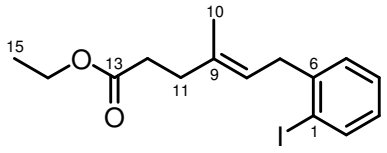


211

Aluminium triisopropoxide (75mg, 0.4mmol) was added in one portion, to a stirred solution of epoxide **217** (100mg, 0.3mmol) in toluene (2ml) at room temperature, under a nitrogen atmosphere. The mixture was heated to reflux for 12h, then cooled to room temperature and diethyl ether (5ml) was added. The mixture was poured onto hydrochloric acid (2M, 5ml) and the separated aqueous phase was then extracted with diethyl ether (3 x 5ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate (10ml), then dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOAc, 95% petrol) on silica gel, to give the alcohol **211** (83mg, 83%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3604 (s), 3468 (br w), 2958 (s), 1651 (m); δ_H (400MHz, $CDCl_3$), 1.57 (1H, d, *J* 9.0Hz, O*H*), 1.86 (3H, s, C=CCH_3, *H*-10), 2.84 (1H, dd, *J* 14.0 and 9.0Hz, ArCH_aH$_b$, *H*-7$_a$), 3.06 (1H, dd, *J* 14.0 and 4.0Hz, ArCH$_a$$H_b$, *H*-7$_b$), 4.36 (1H, app br d, *J* 9.0Hz, HOC*H*, *H*-8), 4.88 (1H, app t, *J* 1.5Hz, C=CH_EH$_Z$, *H*-11$_E$), 5.03 (1H, app t, *J* 1.5Hz, C=CH$_E$$H_Z$, *H*-11$_Z$), 6.92 (1H, ddd, *J* 8.0, 7.0 and 2.0Hz, Ar*H*, *H*-3), 7.22-7.32 (2H, m, 2 x Ar*H*, *H*-4,5), 7.84 (1H, dd, *J* 8.0 and 1.0Hz, Ar*H*, *H*-2); δ_C (100MHz, $CDCl_3$), 18.3 (q, *C*-10), 46.7 (t, *C*-7), 74.8 (d, *C*-8), 101.0 (s, *C*-1), 111.2 (t, C-11), 128.2, 128.4 (2 x d, *C*-3,4), 131.1 (d, *C*-5),

139.7 (d, *C*-2), 141.2 (s, *C*-6), 146.9 (s, C-9); m/z (ES) 310.9892 (M + Na^+, $C_{11}H_{13}O^{127}INa$ requires 310.9909).

***(E)-Ethyl 6-(2-iodophenyl)-4-methylhex-4-enoate* 210**

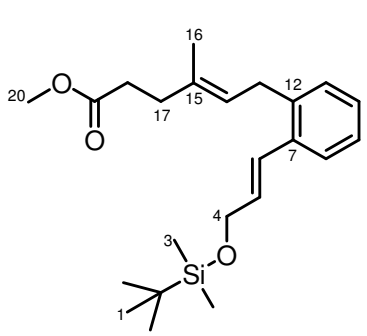


210

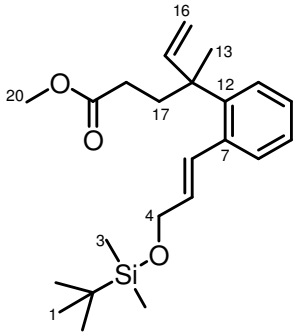
Propionic acid (0.1ml, 1.3mmol) was added dropwise over 2mins, to a stirred solution of the alcohol **211** (2.6g, 9.0mmol) in triethyl orthoacetate (35ml, 185.0mmol) at room temperature under a nitrogen atmosphere. The solution was heated to 100°C under Dean-Stark conditions for 4 days, then cooled to room temperature and concentrated *in vacuo*. Diethyl ether (20ml) and water (20ml) were added, and the separated aqueous phase was then extracted with diethyl ether (3 x 20ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (20ml), then dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (2% EtOAc, 98% petrol) on silica gel, to give the ester **210** (2.9g, 91%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2984 (m), 1727 (s), 1562 (m); δ_H (400MHz, $CDCl_3$), 1.23 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-15), 1.74 (3H, app s, $C{=}CCH_3$, *H*-10), 2.34-2.41 (2H, m, $O{=}CCH_2CH_2$, *H*-11), 2.42-2.48 (2H, m, $O{=}CCH_2CH_2$, *H*-12), 3.41 (2H, d, *J* 7.0Hz, $ArCH_2$, *H*-7), 4.10 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-14), 5.30 (1H, tq, *J* 7.0 and 1.0Hz, C=C*H*, *H*-8), 6.88 (1H, ddd, *J* 8.0, 7.5 and 2.0Hz, Ar*H*, *H*-3), 7.16 (1H, dd, *J* 7.5 and 2.0Hz, Ar*H*, *H*-5), 7.26 (1H, ddd, *J* 8.0, 7.5 and 1.5Hz, Ar*H*, *H*-4), 7.81 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-2); δ_C (100MHz, $CDCl_3$), 14.2 (q, *C*-15), 16.4 (q, *C*-10), 33.1 (t, *C*-12), 34.6 (t, *C*-11), 39.5 (t, *C*-7), 60.3 (t, *C*-14), 100.7 (s, C-1), 122.4 (d, *C*-8), 127.7 (d, *C*-3), 128.3 (d, *C*-4), 129.1 (d,

C-5), 135.5 (s, *C*-9), 138.3 (d, *C*-2), 143.8 (s, *C*-6), 173.3 (s, *C*-13); m/z (ES) 359.0499 ($M + H^+$, $C_{15}H_{20}O_2{}^{127}I$ requires 359.0508).

(4E)-Methyl-6-(2-((E)-3-hydroxy((tert-butyl)dimethylsilane)prop-1-enyl)phenyl)-4-methylhex-4-enoate **200** **and** **(±)*-methyl-4-(2-((E)-3-hydroxy((tert-butyl)dimethylsilane)prop-1-enyl)phenyl)-4-methylhex-5-enoate*** **201**



200



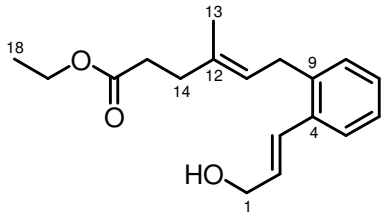
201

n-Butyllithium (2.5M, 14.5ml, 36.3mmol) was added dropwise over 30mins, to a stirred solution of (2-bromocinnamyloxy)(*tert*-butyl)dimethylsilane **199** (11.2g, 34.3mmol) and copper iodide (6.8g, 34.2mmol) in tetrahydrofuran (100ml) at -78°C, under an argon atmosphere. The mixture was stirred at -78°C for 2h, then warmed to -35°C, and stirred at -35°C for 45mins. The mixture was cooled to -45°C and then a solution of (*E*)-methyl 6-bromo-4-methylhex-4-enoate **198** (6.2g, 28.1mmol) in tetrahydrofuran (20ml) was added, *via* canula, over 30mins. The mixture was allowed to warm slowly to room temperature over 15h, and then diethyl ether (100ml) and saturated ammonium chloride (50ml) were added. The separated aqueous phase was extracted with diethyl ether (3 x 20ml) and the combined organic extracts were then washed with brine (50ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOAc, 95% petrol) on silica gel,

to give the esters **200/201** (10.0g, 95%) as an inseparable 8:5 mixture of olefin isomers, as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3010 (s), 2956 (s), 3502 (br w), 1731 (s), 1599 (w); m/z (ES) 411.2331 (M + Na^+, $C_{23}H_{36}O_3SiNa$ requires 411.2326); NMR data for trisubstituted olefin **200**: δ_H (400MHz, $CDCl_3$), 0.12 (6H, s, $OSi(CH_3)_2$, *H*-3), 0.94 (9H, s, $SiC(CH_3)_3$, *H*-1), 1.73 (3H, app s, $C{=}CCH_3$, *H*-16), 2.34 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, *H*-17), 2.44 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, *H*-18), 3.38 (2H, d, *J* 7.0Hz, $ArCH_2$, *H*-13), 3.63 (3H, s, OCH_3, *H*-20), 4.36 (2H, dd, *J* 3.5 and 1.5Hz, OCH_2, *H*-4), 5.29 (1H, tq, *J* 7.0 and 1.0Hz, $H_3CC{=}CH$, *H*-14), 6.15 (1H, dt, *J* 15.5 and 3.5Hz, $ArCH{=}CH$, *H*-5), 6.82 (1H, dt, *J* 15.5 and 1.5Hz, ArC*H*, *H*-6), 7.14-7.32 (3H, m, 3 x Ar*H*, *H*-9,10,11), 7.38 (1H, dd, *J* 7.0 and 1.5 Hz, Ar*H*, *H*-8); δ_C (100MHz, $CDCl_3$), -5.1 (2C q, C-3), 16.2 (q, C-16), 18.4 (s, C-2), 25.9 (3C q, C-1), 31.8 (t, C-18), 34.6 (t, C-17), 34.6 (t, C-13), 51.5 (q, C-20), 64.0 (t, C-4), 123.6 (d, C-14), 126.5 (d, C-5), 127.2 (d, C-9), 127.4 (d, C-8), 127.8 (d, C-10), 129.4 (d, C-11), 130.8 (d, C-6), 134.3, 136.0 (2 x s, C-7,12), 138.5 (s, C-15), 173.8 (s, C-19); NMR data for monosubstituted olefin **201**: δ_H (400MHz, $CDCl_3$), 0.10 (6H, s, $OSi(CH_3)_2$, *H*-3), 0.94 (9H, s, $SiC(CH_3)_3$, *H*-1), 1.43 (3H, s, $C{=}CCH_3$, *H*-13), 2.34 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, *H*-17), 2.43 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, H-18), 3.60 (3H, s, OCH_3, *H*-20), 4.31 (2H, dd, *J* 4.5 and 1.5Hz, OCH_2, *H*-4), 4.97 (1H, dd, *J* 17.0 and 1.0Hz, $HC{=}CH_EH_Z$, *H*-16_E), 5.09 (1H, dd, *J* 10.5 and 1.0Hz, $HC{=}CH_EH_Z$, *H*-16_Z), 5.94 (1H, dt, *J* 15.5 and 4.5Hz, $ArCH{=}CH$, *H*-5), 6.07 (1H, dd, *J* 17.0 and 10.5Hz, $H_2C{=}CH$, *H*-15), 6.84 (1H, dt, *J* 15.5 and 1.5Hz, ArC*H*, *H*-6), 7.09-7.25 (3H, m, 3 x Ar*H*, *H*-9,10,11), 7.44 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-8); δ_C (100MHz, $CDCl_3$), -5.2 (2C q, C-3), 18.4 (s, C-2), 25.9 (3C q, C-1), 26.8 (q, C-14), 29.7 (t, C-18), 32.9 (t, C-17), 44.5 (s, C-13), 51.5

(q, C-20), 63.8 (t, C-4), 112.4 (t, C-16), 126.6 (d, C-5), 126.8 (d, C-9), 127.5 (d, C-8), 127.9 (d, C-10), 129.4 (d, C-11), 131.2 (d, C-6), 138.1 (s, C-7), 142.0 (s, C-12), 146.7 (d, C-15), 174.3 (s, C-19).

***(4E)-Ethyl-6-(2-((E)-3-hydroxyprop-1-enyl)phenyl)-4-methylhex-4-enoate* 226**



226

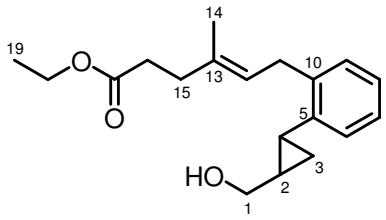
A solution of the aryl iodide **210** (2.50g, 7.0mmol) (or the aryl triflate **246**) and (*E*)-3-(tributylstannyl)prop-2-en-1-ol **225**[117] (2.60g, 7.5mmol) in *N*-dimethylformamide (20ml) was added dropwise over 1min, to flame-dried lithium chloride (0.58g, 13.5mmol) and lithium iodide (1.80g, 13.0mmol) in a Schlenk flask at room temperature, under an argon atmosphere. The mixture was degassed and *bis*-triphenylphosphinepalladium dichloride (0.24g, 0.3mmol) was added in one portion, and the mixture was then degassed again. The mixture was heated to 80^{o}C for 16h, and then cooled to room temperature and poured onto water (50ml) and ethyl acetate (50ml). The separated aqueous phase was extracted with ethyl acetate (3 x 100ml) and the combined organic extracts were then washed with water (3 x 20ml), hydrochloric acid (2M, 10ml) and brine (50ml), dried over sodium sulphate and concentrated *in vacuo* to leave a residue which consisted of a 6:1 mixture of *Z*:*E* olefin isomers of the alkene. Data for *Z*-isomer: δ_H (400MHz, $CDCl_3$), 1.20 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-18), 1.73 (3H, app s, $C{=}CCH_3$, *H*-13), 2.37 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, *H*-14), 2.43 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, *H*-15), 3.36 (2H, d, *J* 7.5Hz, $ArCH_2$, *H*-10), 4.09 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-17), 4.27 (2H, dd, *J* 6.5 and 1.5Hz,

HOCH_2, *H*-1), 5.39 (1H, tq, *J* 7.5 and 1.0Hz, C=C*H*, *H*-11), 5.94 (1H, dt, *J* 11.5 and 6.5Hz, ArCH=C*H*, *H*-2), 6.65 (1H, dt, *J* 11.5 and 1.5Hz, ArC*H*=CH, *H*-3), 7.07 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-8), 7.12-7.20 (2H, m, 2 x Ar*H*, *H*-6,7), 7.46 (1H, dd, *J* 6.5 and 1.5Hz, Ar*H*, *H*-5);

The mixture was dissolved in benzene (50ml), and approximately 10 grains of iodine on silica (iodine adsorbed onto chromatographic silica with dichloromethane) were added. The mixture was left for 12h in direct sunlight, then saturated sodium thiosulphate (50ml) was added and the organic phase was separated and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% Et_2O, 60% petrol) on silica gel, to give the *E*-alcohol **226** (1.25g, 60%) (58% from aryl triflate **246**) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3611 (w), 3502 (br w), 3011 (m), 1725 (s), 1601 (w); δ_H (400MHz, $CDCl_3$), 1.15 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-18), 1.76 (3H, app s, C=CCH_3, *H*-13), 2.34 (2H, t, *J* 7.0Hz, O=CCH_2CH_2, *H*-14), 2.43 (2H, t, *J* 7.0Hz, O=CCH_2CH_2, *H*-15), 3.38 (2H, d, *J* 7.0Hz, ArCH_2, *H*-10), 4.04 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-17), 4.32 (2H, dd, *J* 5.5 and 1.0Hz, HOCH_2, *H*-1), 5.24 (1H, tq, *J* 7.0 and 1.0Hz, C=C*H*, *H*-11), 6.25 (1H, dt, *J* 15.5 and 5.5Hz, ArCH=C*H*, *H*-2), 6.79 (1H, dt, *J* 15.5 and 1.0Hz, ArC*H*=CH, *H*-3), 7.13 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-8), 7.15-7.20 (2H, m, 2 x Ar*H*, *H*-6,7), 7.46 (1H, dd, *J* 6.5 and 1.5Hz, Ar*H*, *H*-5); δ_C (100MHz, $CDCl_3$), 14.1 (q, *C*-18), 16.2 (q, *C*-13), 32.3 (t, *C*-10), 33.0 (t, *C*-15), 34.5 (t, *C*-14), 60.4 (t, *C*-17), 63.9 (t, *C*-1), 123.9 (d, *C*-11), 125.9 (d, *C*-2), 126.3 (d, *C*-6), 127.7 (d, *C*-5), 128.5 (d, *C*-7), 129.3 (d, *C*-8), 130.1 (d, *C*-3), 133.9, 135.6 (2 x s, *C*-4,9), 138.7 (s, *C*-12), 173.4 (s, *C*-16); m/z (ES) 311.1619 (M + Na^+, $C_{18}H_{24}O_3Na$ requires 311.1618).

(E)-Ethyl-6-(2-(2-(hydroxymethyl)cyclopropyl)phenyl)-4-methylhex-4-enoate

227

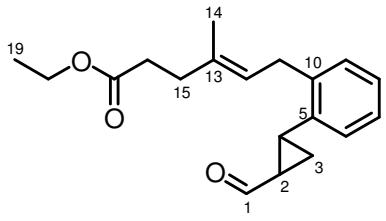


227

Diethylzinc (1.0M in hexanes, 520µl, 0.5mmol) was added dropwise over 20 min, to a stirred solution of the olefin **226** (100mg, 0.3mmol) and diiodomethane (84µl, 1.0mmol) in dichloromethane (10ml) at room temperature, under an argon atmosphere. The mixture was stirred at room temperature for 4h and then more diethylzinc (1.0M in hexanes, 520µl, 0.5mmol) and diiodomethane (84µl, 1.0mmol) were added dropwise, over 20mins. The mixture was stirred at room temperature for 14h and then ethyl acetate (50ml) and water (50ml) were added. The separated aqueous phase was extracted with ethyl acetate (3 x 20ml), and the combined organic extracts were then washed with brine (10ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O, 70% petrol) on silica gel, to give the cyclopropane **227** (86mg, 82%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3613 (w), 3520 (br w), 3009 (m), 1726 (s), 1602 (w); δ_H (400MHz, $CDCl_3$), 0.87-0.94 (2H, m, ArCHCH_2, *H*-3), 1.19 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-19), 1.38-1.45 (1H, m, $HOCH_2CH$, *H*-2), 1.75 (3H, d, *J* 1.0Hz, C=CCH_3, *H*-14), 1.84 (1H, app dt, *J* 9.0 and 5.0Hz, ArC*H*, *H*-4), 2.10 (1H, app br s, O*H*), 2.37 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, *H*-15), 2.44 (2H, t, *J* 7.0Hz, $O{=}CCH_2CH_2$, *H*-16), 3.47 (1H, dd, *J* 16.0 and 7.0Hz, $ArCH_aH_b$, *H*-11_a), 3.53 (1H, dd, *J* 16.0 and 7.0Hz, $ArCH_aH_b$, *H*-11_b), 3.66 (2H, d, *J* 6.5Hz, $HOCH_2$, *H*-1), 4.07 (2H, q, *J* 7.0Hz, OCH_2CH_3, *H*-18), 5.34 (1H, app tq, *J* 7.0

and 1.0Hz, C=C*H*, *H*-12), 6.99 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-6), 7.10-7.15 (3H, m, 3 x Ar*H*, *H*-7,8,9); δ_C (100MHz, $CDCl_3$), 12.0 (t, *C*-3), 14.2 (q, *C*-19), 16.2 (q, *C*-14), 19.0 (d, *C*-4), 23.4 (d, *C*-2), 31.8 (t, *C*-11), 33.1 (t, *C*-16), 34.7 (t, *C*-15), 60.4 (t, *C*-18), 66.6 (t, *C*-1), 123.9 (d, *C*-12), 125.8, 126.1, 126.2 (3 x d, *C*-7,8,9), 128.6 (d, *C*-6), 134.3 (s, *C*-10), 139.6 (s, *C*-13), 140.7 (s, *C*-5), 173.5 (s, *C*-17); m/z (ES) 325.1784 ($M + Na^+$, $C_{19}H_{26}O_3Na$ requires 325.1774).

***(E)-Ethyl 6-(2-(2-formylcyclopropyl)phenyl)-4-methylhex-4-enoate* 228**

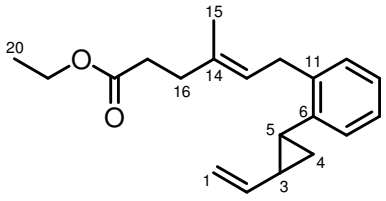


228

2-Iodoxybenzoic acid (2.75g, 9.8mmol) was added portionwise, to a stirred solution of the alcohol **227** (1.85g, 6.1mmol) in dimethylsulfoxide (25ml) at room temperature, under an argon atmosphere. The solution was stirred at room temperature for 12h and then water (25ml) was added. The mixture was filtered through celite using diethyl ether (50ml), and the separated aqueous phase was then extracted with diethyl ether (3 x 20ml). The combined organic extracts were washed with brine (30ml), then dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc, 80% petrol) on silica gel, to give the aldehyde **228** (1.31g, 70%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3011 (m), 1715 (br s), 1603 (w); δ_H (400MHz, $CDCl_3$), 1.21 (3H, t, *J* 7.0Hz, OCH_2CH_3, *H*-19), 1.52-1.58 (1H, m, $ArCHCH_aH_b$, *H*-3_a), 1.67-1.70 (1H, m, $ArCHCH_aH_b$, *H*-3_b), 1.71 (3H, app s, $C=CCH_3$, *H*-14), 2.05 (1H, ddd, *J* 9.0, 7.0 and 5.0Hz, ArC*H*, *H*-4), 2.35 (2H, t, *J* 7.0Hz, $O=CCH_2CH_2$, *H*-15), 2.43 (2H, t, *J* 7.0Hz,

O=CCH_2CH$_2$, *H*-16), 2.62-2.70 (1H, m, O=CHC*H*, *H*-2), 3.42 (2H, d, *J* 7.0Hz, ArCH_2, *H*-11), 4.09 (2H, q, *J* 7.0Hz, OCH_2CH$_3$, *H*-18), 5.28 (1H, tq, *J* 7.0 and 1.0Hz, C=C*H*, *H*-12), 7.00 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-6), 7.12-7.23 (3H, m, 3 x Ar*H*, *H*-7,8,9), 9.34 (1H, d, *J* 5.0Hz, O=C*H*, *H*-1); δ_C (100MHz, $CDCl_3$), 14.1 (q, *C*-19), 15.0 (t, *C*-3), 16.2 (q, *C*-14), 24.3 (d, *C*-4), 31.6 (t, *C*-11), 32.3 (d, *C*-2), 33.0 (t, *C*-16), 34.5 (t, *C*-15), 60.2 (t, *C*-18), 122.9 (d, *C*-12), 125.9, 126.2, 127.1 (3 x d, *C*-7,8,9), 128.8 (d, *C*-6), 134.9 (s, *C*-10), 136.3 (s, *C*-13), 140.9 (s, *C*-5), 173.2 (s, *C*-17), 199.9 (s, *C*-1); m/z (ES) 323.1617 (M + Na^+, $C_{19}H_{24}O_3Na$ requires 323.1618).

***(E)-Ethyl 4-methyl-6-(2-(2-vinylcyclopropyl)phenyl)hex-4-enoate* 209**

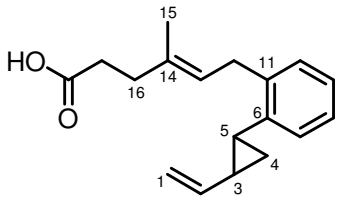


209

Tetrahydrofuran (40ml) was added to freshly dried (100°C, 1mmHg, 5h) methyltriphenylphosphonium bromide (4.3g, 12.0mmol) at room temperature, under an argon atmosphere. A solution of sodium hexamethyldisilazane (1.0M) in THF (5.6ml, 5.6mmol) was added dropwise over 15 min to the stirred solution at -78°C. The mixture was stirred at -78°C for 15 min and then a solution of the aldehyde **228** (1.4g, 4.7mmol) in tetrahydrofuran (20ml) was added dropwise, *via* canula, over 15 min. The mixture was stirred at -78°C for a further 2h and then allowed to warm to room temperature over 12h. Diethyl ether (50ml) and water (50ml) were added, and the separated aqueous phase was then extracted with diethyl ether (3 x 20ml). The combined organic extracts were dried over sodium sulphate and then concentrated *in vacuo*. The residue

was purified by flash column chromatography (5% EtOAc, 95% petrol) on silica gel, to give the alkene **209** (1.3g, 93%) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3011 (s), 1727 (s), 1634 (m), 1602 (w); δ_H (400MHz, $CDCl_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0Hz, ArCHC*H*$_a$H$_b$, *H*-4$_a$), 1.22 (3H, t, *J* 7.0Hz, OCH$_2$C*H*$_3$, *H*-20), 1.24-1.27 (1H, m, ArCHCH$_a$*H*$_b$, *H*-4$_b$), 1.54-1.59 (1H, m, H$_2$C=CHC*H*, *H*-3), 1.72 (3H, app s, C=CC*H*$_3$, *H*-15), 1.96 (1H, ddd, *J* 8.5, 5.5 and 5.0Hz, ArC*H*, *H*-5), 2.36 (2H, t, *J* 7.0Hz, O=CCH$_2$C*H*$_2$, *H*-16), 2.43 (2H, t, *J* 7.0Hz, O=CC*H*$_2$CH$_2$, *H*-17), 3.43 (1H, dd, *J* 16.0 and 7.0Hz, ArC*H*$_a$H$_b$, *H*-12$_a$), 3.49 (1H, dd, *J* 16.0 and 7.0Hz, ArCH$_a$*H*$_b$, *H*-12$_b$), 4.10 (2H, q, *J* 7.0Hz, OC*H*$_2$CH$_3$, *H*-19), 4.96 (1H, dd, *J* 10.0 and 1.5Hz, HC=CH$_E$*H*$_Z$, *H*-1$_Z$), 5.13 (1H, dd, *J* 17.0 and 1.5Hz, HC=C*H*$_E$H$_Z$, *H*-1$_E$), 5.34 (1H, app tq, *J* 7.0 and 1.5Hz, C=C*H*, *H*-13), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5Hz, H$_2$C=C*H*, *H*-2), 6.99 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-7), 7.12-7.15 (3H, m, 3 x Ar*H*, *H*-8,9,10); δ_C (100MHz, $CDCl_3$), 14.2 (q, *C*-20), 14.6 (t, *C*-17), 16.2 (q, *C*-15), 23.0 (d, *C*-5), 25.7 (d, *C*-3), 31.6 (t, *C*-17), 33.2 (t, *C*-16), 34.7 (t, *C*-12), 60.3 (t, *C*-19), 112.4 (t, *C*-1), 123.6 (d, *C*-13), 125.7, 126.0, 126.1 (3 x d, *C*-8,9,10), 128.4 (d, *C*-7), 134.4 (s, *C*-11), 139.5 (s, *C*-14), 140.9 (s, *C*-6), 141.0 (d, *C*-2), 173.4 (s, *C*-18); m/z (ES) 321.1817 (M + Na^+, $C_{20}H_{26}O_2Na$ requires 321.1825).

***(E)-4-Methyl-6-(2-(2-vinylcyclopropyl)phenyl)hex-4-enoic acid* 229**

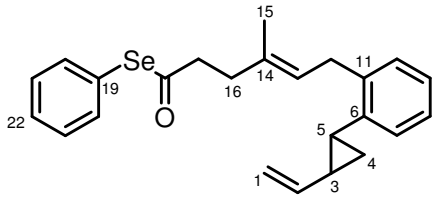


229

A solution of lithium hydroxide (40mg, 1.7mmol) in water (2ml) was added dropwise over 2min, to a stirred solution of the ester **209** (150mg, 0.5mmol) in

acetonitrile (4ml) at room temperature. The mixture was stirred at room temperature for 24h, then diethyl ether (1ml) was added and the separated organic phase was extracted with water (2 x 5ml) and sodium hydroxide (2M, 5ml). Hydrochloric acid (2M) was added to the combined aqueous extracts until pH 1 (approximately 10ml). The acidified aqueous phase was extracted with ethyl acetate (3 x 10ml), and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*, to leave the carboxylic acid **229** (135mg, 96%) as a colourless oil which was used in the next step without further purification; ν_{max}(sol $CHCl_3$)/cm^{-1}, 3059 (s), 2929 (s), 1709 (w), 1600 (m); δ_H (400MHz, $CDCl_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0Hz, ArCHCH_aH_b, *H*-4_a), 1.25 (1H, ddd, J 8.5, 6.0 and 5.0Hz, ArCHCH_aH_b, *H*-4_b), 1.53-1.61 (1H, m, H_2C=CHC*H*, *H*-3), 1.73 (3H, app s, C=CCH_3, *H*-15), 1.96 (1H, ddd, *J* 8.5, 5.5 and 5.0Hz, ArC*H*, *H*-5), 2.37 (2H, t, *J* 7.0Hz, O=CCH_2CH_2, *H*-16), 2.49 (2H, t, *J* 7.0Hz, O=CCH_2CH_2, *H*-17), 3.44 (1H, dd, *J* 16.0 and 7.0Hz, ArCH_aH_b, *H*-12_a), 3.49 (1H, dd, *J* 16.0 and 7.0Hz, ArCH_aH_b, *H*-12_b), 4.96 (1H, dd, *J* 10.0 and 1.5Hz, HC=CH_EH_Z, *H*-1_Z), 5.13 (1H, dd, *J* 17.0 and 1.5Hz, HC=CH_EH_Z, *H*-1_E), 5.37 (1H, app tq, *J* 7.0 and 1.5Hz, C=C*H*, *H*-13), 5.57 (1H, ddd, *J* 17.0, 10.0 and 8.5Hz, H_2C=C*H*, *H*-2), 6.99 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-7), 7.12-7.15 (3H, m, 3 x Ar*H*, *H*-8,9,10); δ_C (100MHz, $CDCl_3$), 14.6 (t, *C*-4), 16.2 (q, *C*-15), 23.0 (d, *C*-5), 25.7 (d, *C*-3), 31.7 (t, *C*-17), 32.7 (t, *C*-16), 34.3 (t, *C*-12), 112.5 (t, *C*-1), 123.8 (d, *C*-13), 125.7, 126.0, 126.1 (3 x d, *C*-8,9,10), 128.5 (d, *C*-7), 134.0 (s, *C*-11), 139.5 (s, *C*-14), 140.8 (s, *C*-6), 141.1 (d, *C*-2), 179.0 (s, *C*-18); m/z (ES) 271.1693 ($M + H^+$, $C_{18}H_{23}O_2$ requires 271.1693).

(E)-Phenyl-4-methyl-6-(2-(2-vinylcyclopropyl)phenyl)hex-4-eneselenoate **193**

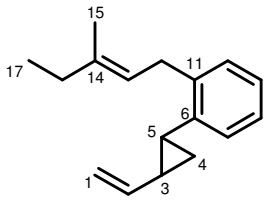


193

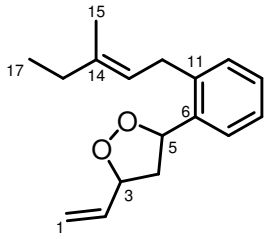
N-Phenylselenylphthalimide (200mg, 0.5mmol) was added, in one portion, to a stirred solution of the carboxylic acid **229** (110mg, 0.4mmol) and tributylphosphine (0.27ml, 1.2mmol) in benzene (1ml) at room temperature, under an argon atmosphere. The mixture was stirred at room temperature for 24h, then poured onto silica and purified by flash column chromatography (100% petrol) on silica gel to give the selenyl ester **193** (90mg, 55%) as a pale yellow oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2924 (m), 1717 (s), 1634 (m); δ_H (400MHz, $CDCl_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0Hz, ArCHC*H*$_a$H$_b$, *H*-4$_a$), 1.26 (1H, ddd, J 8.5, 6.0 and 5.0Hz, ArCHCH$_a$*H*$_b$, *H*-4$_b$), 1.54-1.60 (1H, m, H_2C=CHC*H*, *H*-3), 1.73 (3H, app s, C=CC*H*$_3$, *H*-15), 1.96 (1H, ddd, *J* 8.5, 6.0 and 5.0Hz, ArC*H*, *H*-5), 2.43 (2H, t, *J* 7.5Hz, O=CCH$_2$C*H*$_2$, *H*-16), 2.84 (2H, t, *J* 7.5Hz, O=CC*H*$_2$CH$_2$, *H*-17), 3.44 (1H, dd, *J* 16.0 and 7.0Hz, ArC*H*$_a$H$_b$, *H*-12$_a$), 3.50 (1H, dd, *J* 16.0 and 7.0Hz, ArCH$_a$*H*$_b$, *H*-12$_b$), 4.97 (1H, dd, *J* 10.0 and 1.5Hz, HC=CH$_E$*H*$_Z$, *H*-1$_Z$), 5.14 (1H, dd, *J* 17.0 and 1.5Hz, HC=C*H*$_E$H$_Z$, *H*-1$_E$), 5.38 (1H, app tq, *J* 7.0 and 1.5Hz, C=C*H*, *H*-13), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5Hz, H_2C=C*H*, *H*-2), 7.00 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-7), 7.13-7.16 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.34-7.41 (3H, m, 3 x Ar*H*, *H*-20,22), 7.46-7.51 (2H, m, 2 x Ar*H*, *H*-21); δ_C (100MHz, $CDCl_3$), 14.6 (t, *C*-4), 16.3 (q, *C*-15), 23.0 (d, *C*-5), 25.8 (d, *C*-3), 31.7 (t, *C*-16), 34.9 (t, *C*-12), 46.1 (t, *C*-17), 112.5 (t, *C*-1), 124.4 (d, *C*-13), 125.7, 126.0, 126.1 (3 x d, *C*-8,9,10), 126.4 (s, *C*-19), 128.5 (d, *C*-7), 128.8 (d, *C*-22), 129.3 (2C d, *C*-21), 133.5 (s, *C*-11), 135.8 (2C

d, *C*-20), 139.5 (s, *C*-14), 140.7 (s, *C*-6), 141.1 (d, *C*-2), 199.8 (s, *C*-18); m/z (ES) 433.1031 (M + Na^+, $C_{24}H_{26}O^{80}SeNa$ requires 433.1041).

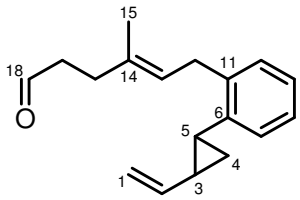
1-((E)-3-Methylpent-2-enyl)-2-(2-vinylcyclopropyl)benzene **230, *3-(2-((E)-3-methylpent-2-enyl)phenyl)-5-vinyl-1,2-dioxolane*** **242, *(E)-4-methyl -6-(2-(2-vinylcyclopropyl)phenyl)hex-4-enal*** **231, *(6E,12E)-8,9,14,15-tetra hydro-7-methyl-5H-benzo[13]annulen-10(11H)-one*** **232, *1,2,4a,5,6,6a,11, 11a-octahydro-11b-methyl-4H-benzo[a]fluoren-3(11bH)-one*** **194 and *(E)-Se-phenyl-4-methyl-6-(2-(5-vinyl-1,2-dioxolan-3-yl)phenyl)hex-4-eneselenoate*** **233**



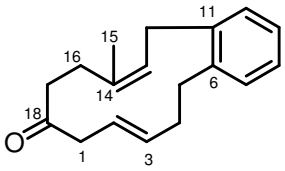
230



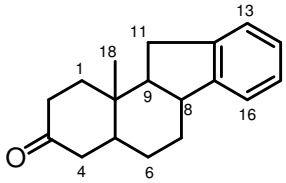
242



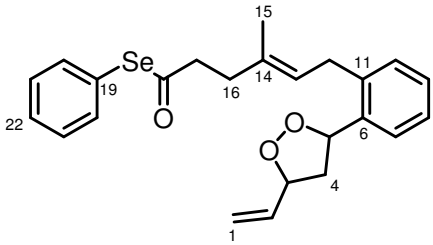
231



232



194



233

A solution of tri-*n*-butyltin hydride (92µl, 0.34mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (2mg, 0.01mmol) in degassed benzene (20ml), was added dropwise over 8h *via* syringe pump, to a stirred solution of the selenyl ester **193** (110mg, 0.26mmol) and 1,1'-azobis(cyclohexanecarbonitrile)

(2mg, 0.01mmol) in degassed benzene (200ml), at 80°C under an argon atmosphere. The mixture was heated under reflux for a further 12h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (0–25% Et_2O, 100-75% petrol) to give: i) the vinylcyclopropane hydrocarbon **230** (<1mg, 1%) (eluted first) as a colourless oil; δ_H (400MHz, $CDCl_3$), 1.01 (3H, t, *J* 7.5Hz, CH_2CH_3, *H*-17), 1.05 (1H, app dt, *J* 8.5 and 5.0Hz, $ArCHCH_aH_b$, *H*-4_a), 1.24-1.32 (1H, m, $ArCHCH_aH_b$, *H*-4_b), 1.50-1.61 (1H, m, $H_2C{=}CHCH$, *H*-3), 1.71 (3H, app s, $C{=}CCH_3$, *H*-15), 1.99 (1H, ddd, *J* 8.5, 6.0 and 5.0Hz, ArC*H*, *H*-5), 2.04 (2H, q, *J* 7.5Hz, CH_2CH_3, *H*-16), 3.44 (1H, dd, J 16.0 and 7.0Hz, $ArCH_aH_b$, *H*-12_a), 3.49 (1H, dd, *J* 16.0 and 7.0Hz, $ArCH_aH_b$, *H*-12_b), 4.95 (1H, dd, *J* 10.0 and 1.5Hz, $HC{=}CH_EH_Z$, *H*-1_Z), 5.13 (1H, dd, *J* 17.0 and 1.5Hz, $HC{=}CH_EH_Z$, *H*-1_E), 5.29 (1H, app tq, *J* 7.0 and 1.5Hz, C=C*H*, *H*-13), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5Hz, $H_2C{=}CH$, *H*-2), 6.98 (1H, dd, *J* 6.0 and 1.5Hz, Ar*H*, *H*-7), 7.11-7.18 (3H, m, 3 x Ar*H*, *H*-8,9,10); upon standing in air, for 5mins, the vinylcyclopropane **230** became oxidised leading to the dioxolane **242** (<1mg, 1%), as a yellow oil; δ_H (400MHz, $CDCl_3$), 1.03 (3H, t, *J* 7.5Hz, CH_2CH_3, *H*-17), 1.75 (3H, app s, $C{=}CCH_3$, *H*-15), 2.06 (2H, q, *J* 7.5Hz, CH_2CH_3, *H*-16), 2.39 (1H, app dt, *J* 12.0 and 7.5Hz, $ArCHCH_aH_b$, *H*-4_a), 3.23 (1H, app dt, *J* 12.0 and 7.5Hz, $ArCHCH_aH_b$, *H*-4_b), 3.35 (1H, dd, J 16.0 and 7.0Hz, $ArCH_aH_b$, *H*-12_a), 3.41 (1H, dd, *J* 16.0 and 7.0Hz, $ArCH_aH_b$, *H*-12_b), 4.89 (1H, app dt, *J* 7.5 and 7.0Hz, $H_2C{=}CHCH$, *H*-3), 5.21 (1H, app tq, *J* 7.0 and 1.5Hz, C=C*H*, *H*-13), 5.30 (1H, dd, *J* 10.0 and 1.5Hz, $HC{=}CH_EH_Z$, *H*-1_Z), 5.41 (1H, dd, *J* 17.0 and 1.5Hz, $HC{=}CH_EH_Z$, *H*-1_E), 5.55 (1H, app t, *J* 7.5Hz, ArC*H*, *H*-5), 5.93 (1H, ddd, *J* 17.0, 10.0 and 7.0Hz, $H_2C{=}CH$, *H*-2), 7.19 (1H, dd, *J* 6.0 and 1.5Hz,

Ar*H*, *H*-7), 7.25-7.31 (3H, m, 3 x Ar*H*, *H*-8,9,10); ii) the saturated aldehyde **231** (3mg, 4%) (eluted second) as a yellow oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2928 (s), 1720 (s), 1634 (m), 1605 (m); δ_H (400MHz, $CDCl_3$), 1.05 (1H, app dt, *J* 8.5 and 5.0Hz, ArCHCH_aH$_b$, *H*-4$_a$), 1.24-1.28 (1H, m, ArCHCH$_a$$H_b$, *H*-4$_b$), 1.52-1.63 (1H, m, H_2C=CHC*H*, *H*-3), 1.73 (3H, d, *J* 1.0Hz, C=CCH_3, *H*-15), 1.95 (1H, ddd, *J* 8.5, 6.0 and 5.0Hz, ArC*H*, *H*-5), 2.38 (2H, t, *J* 7.5Hz, O=CCH$_2$CH_2, *H*-16), 2.56 (2H, td, *J* 7.5 and 2.0Hz, O=CCH_2CH$_2$, *H*-17), 3.45 (1H, dd, *J* 16.0 and 7.0Hz, ArCH_aH$_b$, *H*-12$_a$), 3.49 (1H, dd, *J* 16.0 and 7.0Hz, ArCH$_a$$H_b$, *H*-12$_b$), 4.96 (1H, dd, *J* 10.0 and 1.5Hz, HC=CH$_E$$H_Z$, *H*-1$_Z$), 5.13 (1H, dd, *J* 17.0 and 1.5Hz, HC=CH_EH$_Z$, *H*-1$_E$), 5.35 (1H, tq, *J* 7.0 and 1.0Hz, C=C*H*, *H*-13), 5.58 (1H, ddd, *J* 17.0, 10.0 and 8.5Hz, H_2C=C*H*, *H*-2), 7.00 (1H, dd, *J* 6.0 and 2.0Hz, Ar*H*, *H*-7), 7.11-7.17 (3H, m, 3 x Ar*H*, *H*-8,9,10), 9.77 (1H, t, *J* 2.0Hz, O=C*H*, *H*-18); m/z (ES) 277.1565 (M + Na^+, $C_{18}H_{22}ONa$ requires 277.1568); recovered starting selenyl ester **193** (5mg, 5%); iii) the macrocyclic dienone **232** (15mg, 22%) (eluted third) as a colourless oil; ν_{max}(sol $CHCl_3$)/cm^{-1}, 2920 (s), 1710 (s), 1605 (w); δ_H (400MHz, $CDCl_3$), 1.72 (3H, d, *J* 1.5Hz, HC=CCH_3, *H*-15), 2.33 (2H, app dd, *J* 6.0 and 4.5Hz, O=CCH$_2$CH_2, *H*-16), 2.48 (2H, app dtd, *J* 7.5, 5.5 and 1.0Hz, ArCH$_2$CH_2, *H*-4), 2.51 (1H, app d, *J* 12.0Hz, O=CCH_aH$_b$CH$_2$, *H*-17$_a$), 2.52 (1H, app td, *J* 4.5 and 1.0Hz, O=CCH$_a$$H_bCH_2$, *H*-17$_b$), 2.69 (1H, app d, *J* 5.5Hz, ArCH_aCH$_b$CH$_2$, *H*-5$_a$), 2.70 (1H, app dd, *J* 6.0 and 5.5Hz, ArCH$_a$CH_bCH$_2$, *H*-5$_b$), 2.91 (2H, app dd, *J* 7.0 and 1.0Hz, O=CCH_2, *H*-1), 3.27 (2H, app d, *J* 7.0Hz, ArCH_2CH=C, *H*-12), 5.05 (1H, app tq, *J* 7.0 and 1.5Hz, ArCH$_2$C*H*=C, *H*-13), 5.26 (1H, app dtt, *J* 15.5, 7.5 and 1.0Hz, O=CCH$_2$CH=C*H*, *H*-3), 5.47 (1H, app dtt, *J* 15.5, 7.0 and 1.0Hz, O=CCH$_2$C*H*=CH, *H*-2), 7.07-7.12 (2H, m, 2 x Ar*H*, *H*-7,8), 7.17 (1H, ddd, *J*

7.5, 7.0 and 2.0Hz, Ar*H*, *H*-9), 7.24 (1H, dd, J 7.5 and 1.0Hz, Ar*H*, *H*-10); δ_C (100MHz, $CDCl_3$), 17.1 (q, *C*-15), 31.0 (t, *C*-12), 32.3 (t, *C*-16), 32.7 (t, *C*-5), 33.7 (t, *C*-4), 40.1 (t, *C*-17), 45.1 (t, *C*-1), 121.2 (d, *C*-13), 125.0 (d, *C*-2), 126.0, 126.3 (2 x d, *C*-8,9), 128.7 (d, *C*-7), 130.2 (d, *C*-10), 131.9 (s, *C*-11), 134.6 (d, *C*-3), 139.0 (s, *C*-14), 139.8 (s, *C*-6), 207.9 (s, *C*-18); m/z (ES) 277.1575 (M + Na^+, $C_{18}H_{22}ONa$ requires 277.1568); iv) a 1:1 mixture of angular methyl epimers of the tetracyclic ketone **194** (15mg, 22%) (eluted fourth) as a crystalline solid m.p 128-129°C (Ethanol); ν_{max}(sol $CHCl_3$)/cm^{-1}, 2928 (s), 1704 (s); The epimers were separated by reverse phase preparative HPLC (MeCN:H_2O) and showed the following data: *trans*, *anti*, *trans* isomer **194a** (present together with ~20% of other epimer impurity) δ_H (400MHz, $CDCl_3$), 1.13 (3H, s, C*H*$_3$, *H*-18), 1.36 (1H, dddd, *J* 12.5, 12.0, 12.0 and 4.5Hz, ArCHC*H*$_{ax}$H$_{eq}$, *H*-7$_{ax}$), 1.43-1.53 (1H, m, O=CCH$_2$CHC*H*$_a$H$_b$, *H*-6$_a$), 1.51-1.60 (1H, m, O=CH$_2$C*H*$_{ax}$H$_{eq}$, *H*-1$_{ax}$), 1.56-1.62 (1H, m, O=CCH$_2$CHCH$_a$*H*$_b$, *H*-6$_b$), 1.60-1.68 (1H, m, O=CCH$_2$C*H*, *H*-4), 1.67 (1H, ddd, *J* 12.5, 12.0 and 7.0, ArCHC*H*, *H*-9), 1.96 (1H, ddd, *J* 13.0, 6.5 and 2.0Hz, O=CCH$_2$CH$_{ax}$*H*$_{eq}$, *H*-1$_{eq}$), 2.21 (1H, ddd, *J* 14.5, 4.0 and 2.0Hz, O=CCH$_{ax}$*H*$_{eq}$CH, *H*-4$_{eq}$), 2.31 (1H, dd, *J* 14.5 and 13.5Hz, O=CC*H*$_{ax}$H$_{eq}$CH, *H*-4$_{ax}$), 2.34-2.42 (2H, 2 x m, O=CCH$_{ax}$*H*$_{eq}$CH$_2$, *H*-2$_{eq}$ + ArCHCH$_{ax}$*H*$_{eq}$, *H*-7$_{eq}$), 2.49 (1H, ddd, *J* 15.0, 13.5 and 6.5Hz, O=CCH$_{ax}$*H*$_{eq}$CH$_2$, *H*-2$_{eq}$), 2.65 (1H, dd, *J* 14.0 and 12.0Hz, ArC*H*$_{ax}$H$_{eq}$, *H*-11$_{ax}$), 2.73 (1H, dd, *J* 14.0 and 7.0Hz, ArCH$_{ax}$*H*$_{eq}$, *H*-11$_{eq}$), 2.93 (1H, ddd, *J* 12.5, 12.0 and 3.5Hz, ArC*H*, *H*-8), 7.12-7.17 (3H, m, 3 x Ar*H*, *H*-14,15,16), 7.23 (1H, dd, *J* 7.0 and 2.0Hz, Ar*H*, *H*-13); δ_C (100MHz, $CDCl_3$), 11.6 (q, *C*-18), 28.8 (t, *C*-7), 29.5 (t, *C*-6), 31.3 (t, *C*-11), 35.6 (s, *C*-10), 38.0 (t, *C*-2), 38.4 (t, *C*-1), 44.0 (d, *C*-8), 44.3 (t, *C*-4), 46.6 (d, *C*-5), 60.7 (d, *C*-9),

122.0 (d, *C*-16), 124.6 (d, *C*-13), 126.2 (2 x d, *C*-14,15), 143.0 (s, *C*-12), 146.6 (s, *C*-17), 211.4 (s, *C*-3); *cis*, *syn*, *trans* isomer **194b** δ_H (400MHz, $CDCl_3$), 1.33 (1H, dddd, *J* 14.5, 13.0, 12.0 and 3.5Hz, ArCHC$H_{ax}H_{eq}$, *H*-7_{ax}), 1.37 (3H, s, CH_3, *H*-18), 1.45 (1H, dddd, *J* 14.0, 13.0, 12.5 and 3.5Hz, O=CCH_2CHC$H_{ax}H_{eq}$, *H*-6_{ax}), 1.66-1.72 (1H, m, O=C$CH_2CH_{ax}H_{eq}$, *H*-1_{eq}), 1.68-1.74 (1H, m, O=CCH_2CH$CH_{ax}H_{eq}$, *H*-6_{eq}), 1.81 (1H, ddd, *J* 12.5, 12.0 and 6.5Hz, ArCHC*H*, *H*-9), 1.81-1.89 (1H, m, ArCH_2C*H*, *H*-5), 2.10 (1H, ddd, *J* 14.5, 2.5 and 2.0Hz, O=CCH_aH_bCH, *H*-4_a), 2.17 (1H, ddd, *J* 14.0, 13.5 and 5.0Hz, O=C$CH_2C H_{ax}H_{eq}$, *H*-1_{ax}), 2.29-2.36 (1H, m, O=C$CH_{ax}H_{eq}CH_2$, *H*-2_{eq}), 2.32-2.38 (1H, m, ArCHC$H_{ax}H_{eq}$, *H*-7_{eq}), 2.53 (1H, dddd, *J* 14.5, 14.0, 7.0 and 0.5Hz, O=CC$H_{ax}H_{eq}CH_2$, *H*-2_{ax}), 2.56 (1H, dd, *J* 14.0 and 12.5Hz, ArC$H_{ax}H_{eq}$, *H*-11_{ax}), 2.81 (1H, dd, *J* 14.0 and 6.5Hz, Ar$CH_{ax}H_{eq}$, *H*-11_{eq}), 2.82 (1H, dd, *J* 14.5 and 12.0Hz, ArC*H*, *H*-8), 2.87 (1H, ddd, *J* 14.5, 6.5 and 0.5Hz, O=CCH_aH_bCH, *H*-4_b), 7.11-7.18 (3H, m, 3 x Ar*H*, *H*-14,15,16), 7.23 (1H, dd, *J* 7.0 and 2.0Hz, Ar*H*, *H*-13); δ_C (100MHz, $CDCl_3$), 24.8 (q, *C*-18), 27.1 (t, *C*-1), 29.2 (t, *C*-7), 30.2 (t, *C*-6), 31.7 (t, *C*-11), 35.1 (s, *C*-10), 37.5 (t, *C*-2), 43.2 (d, *C*-8), 44.2 (t, *C*-4), 46.2 (d, *C*-5), 59.8 (d, *C*-9), 122.0 (d, *C*-16), 124.5 (d, *C*-13), 126.1 (2 x d, *C*-14,15), 143.0 (s, *C*-12), 146.6 (s, *C*-17), 212.1 (s, *C*-3); m/z (ES) 277.1570 ($M + Na^+$, $C_{18}H_{22}ONa$ requires 277.1568); a small amount of starting phenyl seleno ester **193** (5%) was also recovered, together with the corresponding dioxolane **233** (10mg, 8%) (eluted last) as a colourless oil; δ_H (400MHz, $CDCl_3$), 1.74 (3H, d, *J* 0.5Hz, HC=CCH_3, *H*-15), 2.36 (1H, app dt, J 12.0 and 7.0Hz, ArCHCHaHb, H-4a), 2.42 (2H, t, *J* 7.5Hz, O=C$CH_2C H_2$, *H*-16), 2.83 (2H, t, *J* 7.5Hz, O=CCH_2CH_2, *H*-17), 3.18 (1H, app dt, J 12.0 and 7.5Hz, ArCHCHaHb, H-4b), 3.34 (1H, dd, *J* 16.0 and 7.0Hz, ArCH_aH_b, *H*-12_a), 3.39

(1H, dd, *J* 16.0 and 7.0Hz, $ArCH_aH_b$, *H*-12_b), 4.85 (1H, app dtt, J 7.5, 7.0 and 1.0Hz, H_2C=CHCH, H-3), 5.27 (1H, app dt, *J* 10.0 and 1.0Hz, HC=CH_EH_Z, *H*-1_Z), 5.28 (1H, app tq, *J* 7.0 and 0.5Hz, C=C*H*, *H*-13), 5.38 (1H, app dt, *J* 17.0 and 1.0Hz, HC=C$H_E$$H_Z$, *H*-$1_E$), 5.49 (1H, app t, J 7.5Hz, ArCH, H-5), 5.89 (1H, ddd, *J* 17.0, 10.0 and 7.5Hz, H_2C=C*H*, *H*-2), 7.14 (1H, dd, *J* 7.5 and 1.5Hz, Ar*H*, *H*-7), 7.33-7.40 (3H, m, 3 x Ar*H*, *H*-8,9,10), 7.44-7.47 (3H, m, 3 x Ar*H*, *H*-20,22), 7.57 (2H, dd, J 7.5 and 7.0Hz, 2 x Ar*H*, *H*-21); δ_C (100MHz, $CDCl_3$), 16.3 (q, *C*-15), 31.5 (t, *C*-16), 34.8 (t, *C*-12), 45.9 (t, *C*-17), 48.8 (t, C-4), 79.6 (d, C-5), 82.3 (d, C-3), 119.0 (t, C-1), 124.2 (d, *C*-13), 125.7, 126.7, 128.1, 128.9 (4 x d, *C*-7,8,9,10), 126.4 (s, *C*-19), 129.3 (2C d, *C*-21), 129.4 (d, C-22), 134.0 (s, *C*-11), 135.0 (d, C-2), 135.7 (2C d, *C*-20), 136.7 (s, *C*-14), 138.4 (s, *C*-6), 199.7 (s, *C*-18); m/z (ES) 465.0956 (M + Na^+, $C_{24}H_{26}O_3{}^{80}SeNa$ requires 465.0945).

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